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ORIGINAL ARTICLES

MEASLES ENCEPHALITIS

Clinical and Electroencephalographic Study

By MELCHIJAH SPRAGINS, M.D., BURTON M. SHINNERS, M.D., AND BETSEY ROCHESTER, A.B.
Buffalo, N.Y.

MUCH has been written in recent years concerning the manifestations of the encephalitis complicating rubella. In spite of the careful studies of Ford,[1] Smith and Trapp,[2] Litvak and his coworkers[3] and others,[4-10] there remains the difficult problem of evaluating the behavior difficulties in these children which follow so frequently after the subsidence of acute symptoms. What part does organic damage of the nervous system contribute, and to what extent do environmental factors explain the personality changes following encephalitis? With this problem in mind, the following study was undertaken in an attempt to correlate the clinical state of the patients with the electroencephalographic patterns observed at different stages in the disease.

The data presented are drawn from a study of 31 cases of rubella complicated by encephalitis admitted to the Children's Hospital of Buffalo during the period of six months from February to July 1946 inclusive. The great majority of these cases arrived at this hospital within 24 hours after the onset of their initial symptoms of encephalitis, and the remainder arrived within a period of a few days. One case was admitted 18 days after onset.

In this series of cases, two patients died and came to autopsy. Suffice it to say that the pathologic examination revealed the typical perivascular myelin destruction with microglial phagocytosis. One of these patients showed the interesting superimposed complication of complete thrombosis of the entire superior sagittal sinus, extending into its tributary vessels.*

From the Children's Hospital of Buffalo and the Department of Pediatrics, University of Buffalo School of Medicine, Buffalo, N.Y.

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* Postmortem examinations performed by Dr. Kornel Terplan, University of Buffalo Department of Pathology.

Age Incidence: By referring to Chart 1 it is seen that the age range of this group is from 1 to 16 years with one half of the cases occurring between 1 and 5 years and the average age being 6.2 years. This approximates fairly closely the age incidence of other reported series.

Acute Symptomatology: The clinical diagnosis of encephalitis complicating rubella was based upon the close association of the onset of central nervous system symptoms with the presence or recent precedence of the measles rash. A predominantly lymphocytic cellular response was demonstrated in the spinal fluid of 28 cases; only 2 patients had normal

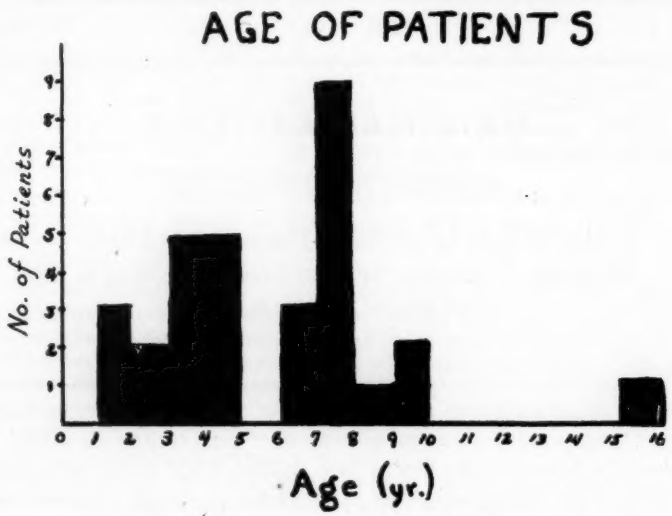

CHART 1. Age incidence of encephalitis in 31 patients.

spinal fluid findings in all respects. As has been pointed out by Litvak et al.,[3] absence of pleocytosis is not an uncommon finding.

Using the appearance of the rash as a point of reference, one sees the average number of days to the onset of nervous system symptoms was approximately 6.6; whereas, the median was 5.5 (Chart 2). The longest interval observed was 21 days. One of the patients had the onset of central nervous system symptoms four days before the appearance of the rash.

The symptoms of onset were highly variable, but grossly may be classified as demonstrated in Table I. All patients showed definite change in the state of consciousness, varying from mild drowsiness to the depths of coma. The incidence of convulsive activity was high, involving more than half the group. Upon examination of the neurologic system, signs of meningeal irritation were prominent. Equally so were signs of pyramidal tract involvement, such as ankle clonus, positive Babinski reflex, spasticity, hyperactive reflexes and absent abdominal and cremasteric reflexes. Pupillary changes were manifested as anisocoria or widely dilated pupils unresponsive to light or accommodation. Less commonly occurring signs were flaccidity, mixed reflex changes, nystagmus, rumination and hyperesthesia.

Duration of Acute Symptoms: One amazing aspect of this disease is the rapidity of

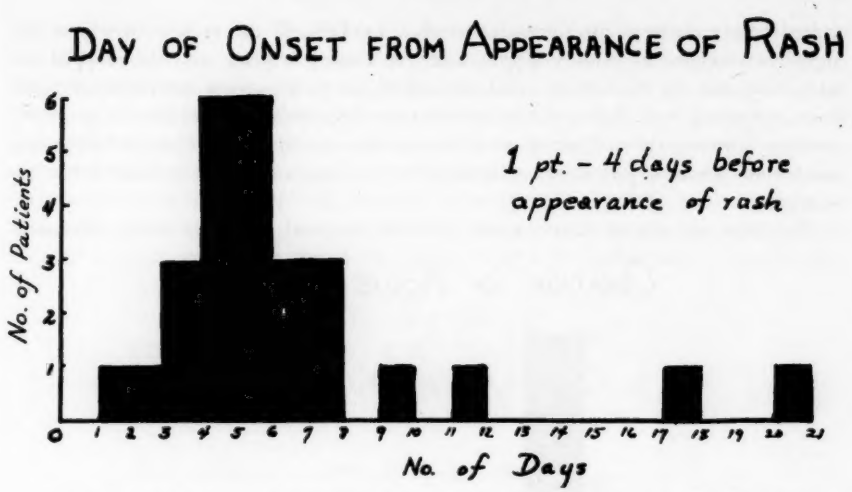

CHART 2. Day of onset of encephalitic symptoms as related to appearance of measles rash.

disappearance of the acute symptoms. This is graphically demonstrated in Chart 3. Four patients were over their acute symptoms within 24 hours, 2 within 48 hours, and 6 within 3 days. Within 7 days 21 patients had recovered. There seems to be no relationship between the severity or type of onset and the duration of the acute symptoms. However, if one carefully evaluates and follows the level of the stage of consciousness of the patient as it returns to normal, a fairly accurate prognosis may be offered as to the future occurrence of severe residua. This is demonstrated in Chart 4.

Residual Symptoms: Of the 31 acute cases, 16 have been followed over the subsequent two years. It should be mentioned that this group is somewhat weighted toward those patients with residua, for those mothers with injured children were the most easily con-

TABLE I

CLINICAL CLASSIFICATION AND INCIDENCE OF SYMPTOMS AND SIGNS OF ACUTE STAGE OF ENCEPHALITIS

Symptoms and Signs of Onset	
Symptoms	
1. Changes of State of Consciousness	31
a. Coma	8
b. Semi-coma	9
c. Delirium	6
d. Drowsiness	8
2. Convulsions	17
a. Clonic	14
b. Jacksonian	3
c. Tonic	2
3. Signs of Meningeal Irritation	19
4. Signs of Pyramidal Tract Involvement	21
5. Pupillary Changes	8

vinced of the necessity for follow-up studies. In Table II the various symptoms and signs are tabulated at periods approximately one and two years after the onset of the acute symptoms. At the time of tabulation, 12 of the patients show definite residua and 4 are completely well. It is apparent that the most frequent and serious chronic symptoms are those affecting the individual's readjustment to his social milieu. Thus, one often may not become aware of the child's difficulties until he has been returned to his home environment.

The great majority of these patients showed emotional instability which was mani-

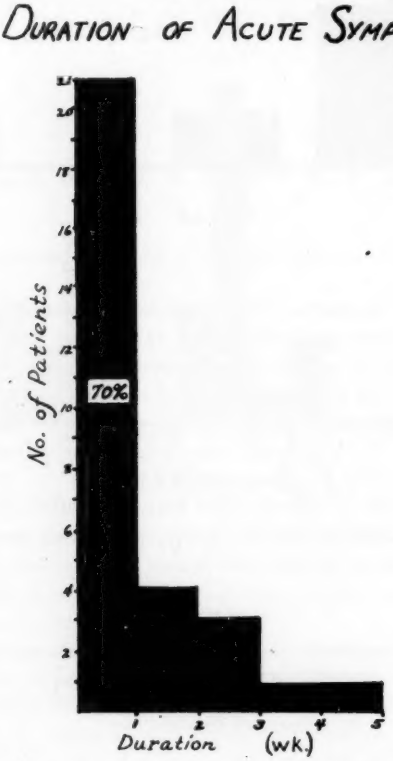

CHART 3. Duration and rate of subsidence of acute encephalitic symptoms.

fested in a variety of ways. Episodes of "tearful anger" were frequent in occurrence, being initiated by anything which obstructed their immediate desires. Fortunately these fits of anger were of short duration and rapidly forgotten. However, during the period of anger they could be destructive to furniture as well as aggressively combative. Impatience was pronounced. Having to wait for anyone or anything was an almost unbearable task. The unpredictability of their behavior under varying circumstances was outstanding.

Memory defects consisted of spotty losses for both past and recent events, complete loss for recent events, and complete loss for past events. The most commonly occurring defect was inability to remember recent events. A remarkable tendency toward improvement in this difficulty existed.

Disturbance of concentration was present in half of the injured children. These chil-

dren, who were at an age where they should have been able to carry out a given task to its completion, were without persistence. Also they were unable to play consistently, jumping from one toy to the next, spending very little time with any toy. During the first year of convalescence those children who returned to school were inattentive, easily diverted from their work, and generally problems to the teacher. It is interesting that of the seven children attending school, the grades of only three were poorer than on previous occasions. This was doubtless influenced by the benign attitude of the teachers who were aware that they were dealing with children recovering from an illness. During the second year of convalescence all but two of the children made a perceptible improvement in their

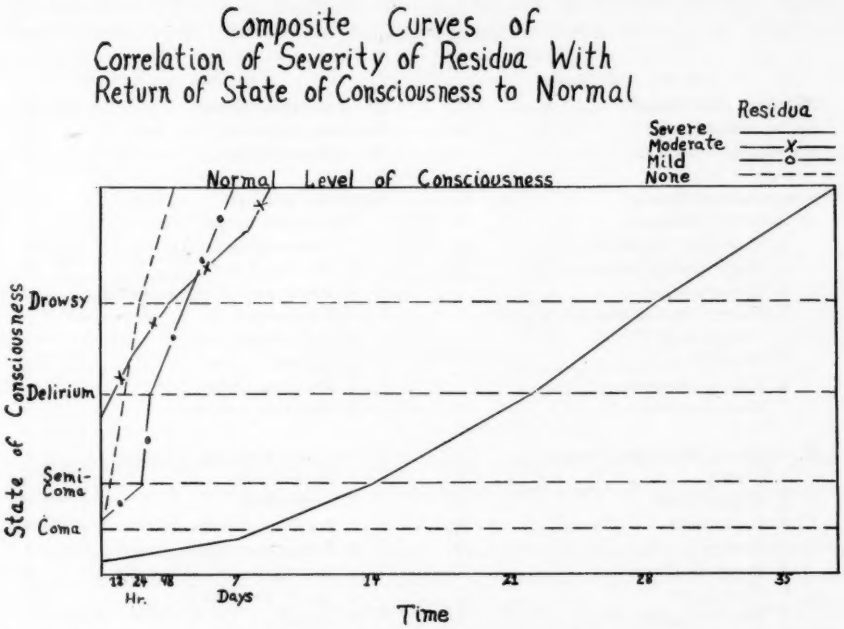

CHART 4. Correlation of rate of disappearance of acute encephalitic symptoms with eventual appearance of residual symptoms and their severity.

school work, some even to the point of excellence. Of the two who did not improve, one was mentally retarded before the onset of his disease, and the other represented such a serious behavior problem that expulsion from school was necessary.

Of the other less common subjective changes, fabrication developed in two patients. It is interesting that these children lied pointlessly and apparently without motivation. Although this characteristic persisted, there was considerable improvement. One child who was originally an out-going, extroverted type of individual, during his first year of convalescence became quite withdrawn and seemed at ease only with his parents. This completely disappeared during the second year and the child was able to form good relationships with other people. On the other hand, another child who was a retiring type became one who talked incessantly, a veritable "chatter box." Sleep disturbance occurred in only one individual and was primarily difficulty in going to sleep. Once asleep, the child rested undisturbed. Obvious mental retardation occurred in only two patients of

whom one made slight improvement and the other remained in a state of arrested development.

A variety of objective neurologic residua were found in this small group of 12 patients. Hyperactivity was the most frequent finding. During their waking hours they seemed to be in constant motion, unable to sit quietly and constantly jumping from one thing to the next. Wringing of the hands and fingernail biting were a part of this difficulty. Four

TABLE II

CLINICAL CLASSIFICATION AND INCIDENCE OF RESIDUAL SYMPTOMS IN 16 PATIENTS FOLLOWED FOR 2 YR. COMPARISON OF FINDINGS DURING 1ST YR. OF CONVALESCENCE WITH THOSE DURING 2ND YR.

Residual Symptoms			
7–10 Mo. after Onset		2 Yr. after Onset	
No. of patients followed	15	No. of patients followed	16
No. of residua	12	No. with residua	12
No. without residua	3	No. without residua	4
Symptoms and Signs	No.	Symptoms and Signs	No.
I. Subjective Changes	11	I. Subjective Changes	11
1. Emotional instability	10	1. Emotional instability	11
2. Disturbance of concentration	4	2. Memory defect	7
3. Memory defect	3	3. Disturbance of concentration	6
4. Poorer school grades (no. attending school—7)	3	4. Fabrication	2
5. Fabrication	2	5. Sleep disturbance	1
6. Fear of strangers	1	6. Obsessive traits	1
7. Sleep disturbance	1	7. Malicious traits	1
		8. Mental retardation	2
II. Objective Neurologic Changes	8	II. Objective Neurologic Changes	9
1. Tremor	4	1. Hyperactivity	6
2. Hyperactivity	4	2. Convulsions	4
3. Convulsions	3	3. Pupillary changes	3
4. Paralysis	2	4. Paralysis or paresis	2
5. Recurrent drowsiness	1	5. Disturbance in penmanship	2
6. Contracture	1	6. Speech impairment	1
7. Impaired speech	1	7. Tremor	1
8. Dilatation of pupils	1		

patients showed persistent tremor in the form of a fine, rapid, intention tremor, which progressively improved. At the end of two years only one showed tremor associated with fatigue while two patients revealed difficulty with penmanship. Four children had residual convulsive activity; three developed this difficulty during the first six months of convalescence in the form of grand mal and petit mal convulsions. The fourth child developed falling attacks without loss of consciousness two years after the onset of his illness. Persistent pupillary changes were manifested in the form of anisocoria (one patient) and dilated pupils with failure of response to accommodation (two patients). Two patients were left with hemiplegia and originally completely useless extremities on the involved side. However, both regained almost complete function and were able to walk, run, dress and feed themselves without difficulty.

In general, one is startlingly impressed with the outstanding tendency of these injured children to improve. All phases of their residual difficulties improve, but it is the objective neurologic changes which show the most rapid recovery, many to complete disappearance.

Electroencephalographic Findings

In this series the initial EEG was taken from 2 to 39 days after the onset of the illness. Seventeen of these records were taken within 2 weeks after onset, 4 within 3½ weeks and 1 within 5½ weeks. A total of 22 initial records were taken. Follow-up records were made each time the patients returned for clinical examination and re-evaluation. In Table III the abnormal findings are tabulated. During the early phase of the disease the EEG usually showed definite slowing of the electric activity to 2-3/sec. waves with superimposed fast activity in the form of low voltage 18-24/sec. waves. A few cases showed a profound depression of activity. As these latter cases improved, their tracings showed the appearance of the slow base line sway and the superimposed fast activity, typical of the group. Other less frequent findings were depressed voltage, high voltage and

TABLE III

Classification of Electroencephalographic Changes During Acute Phase of Encephalitis, During 1st Yr. of Convalescence and at End of 2 Yr. of Convalescence

	Electroencephalographic Changes	
Initial Changes 22 EEGs taken	Follow-up Findings (7–10 mo.) 15 EEGs taken	Follow-up Findings (2 yr.) 16 EEGs taken
1. Slow wave activity 20	1. Slow wave activity 8	1. Slow wave activity 10
1. Without hyperventilation ... 15	1. Without hyperventilation ... 1	1. Without hyperventilation ... 4
2. After hyperventilation 5	2. After hyperventilation 7	2. After hyperventilation 6
2. Fast activity 18	2. Fast activity 8	2. Fast activity 7
3. Depressed voltage 9	3. Depressed voltage 1	3. Hemisphere asymmetry 3
4. High voltage 1	4. High voltage 1	4. Focus 2
5. Normal 2	5. Hemisphere asymmetry 1	5. Depressed voltage 1
	6. Focus 1	6. Normal 2
	7. Normal 1	7. Unsatisfactory 1
	8. Unsatisfactory 2	

slowing with hyperventilation, and high voltage without hyperventilation. Two of the initial EEGs were normal at the time at which they were recorded—10 and 20 days after onset, respectively.

During the convalescent period as improvement occurred clinically, improvement was shown in the EEG. This was demonstrated in the gradual disappearance of slow wave activity and depressed voltage. The normal wave pattern for the age reappeared. With passage of time one of the most persistent findings was the fast activity appearing in varying degree from almost total involvement of the record to intermittent but frequent bursts. Not uncommon was slow wave activity and hemisphere asymmetry. Considerable electric instability was brought out by hyperventilation, resulting in marked slowing of the tracing with high voltage. Foci of abnormal discharges appeared in two records. One patient developed the typical spike and wave pattern of petit mal during a period of hyperventilation 23 days after onset of his illness. Under therapy with sodium 5,5-diphenylhydantoinate (dilantin sodium®) this was not again demonstrated. Only one patient showed the persistence of depressed voltage and this is of a severe degree. Two records two years after onset of disease are now entirely normal.

As demonstrated in Chart 5, an attempt is made to correlate the clinical picture and the EEG. A gross classification of both the clinical picture and the EEG are made under the broadly descriptive terms of mild, moderate and severe. In the acute cases the terms refer to the depth of the state of consciousness, persistence of convulsive activity and rapidity of disappearance of acute symptoms. In the study of residual affliction, the terms refer to severity of changes in the personality, extensiveness of memory defect and extent

of neurologic defects. In the EEG severe refers to marked slowing of the record and/or the extensive occurrence of fast activity. Mild refers to fast activity or slow wave activity appearing in short bursts here and there throughout the various leads with the basic wave pattern either normal or approximating normality. It is seen that at the time of the initial EEG there is the tendency for the EEG to show more severe changes than one would suspect from observing the clinical picture. In the follow-up series, there is an approximate straight-line correlation between clinical severity and EEG changes. It is of importance

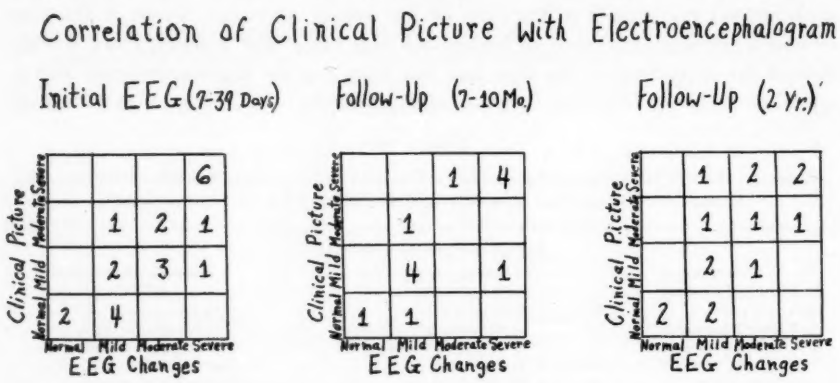

CHART 5. Comparison of degree of severity of clinical manifestations of encephalitis with degree of changes in EEG.

to note that in both the initial and follow-up studies several cases occur which are classified as normal clinically but still show definite persistent electroencephalographic changes.

DISCUSSION

As previously demonstrated, personality changes are paramount as the child attempts to reintegrate himself following the vicious onslaught of this disease. The major problem facing these children is readjustment to their social environment. The degree of emotional maladjustment is a function of the severity of organic damage and the duress of existing environmental factors. The fact that there occur inconsistencies in behavior depending upon environmental situations has been observed repeatedly in this group of patients as well as by other students of the brain-injured child.[2,4,5] Some of the adverse environmental factors stem directly from the child's illness, such as the almost universal overprotectiveness of the parent, rupture of the family resulting in separation of the parents, financial embarrassment, and social embarrassment of parents for having an unusual child. Conversely, the child must establish relationships with individuals who fail to realize that they are dealing with a sick child because he has no obvious signs of crippling. Usually these individuals are overly severe in the management of the child. So also are the child's playmates who with painful accuracy point out and accentuate the injured child's difficulties. These are but a few of the many major hazards facing the child in his rehabilitation. No attempt is being made to minimize the part played by organic damage; for it is fully realized that these children are suffering from perceptual difficulties as well as peculiarities of thinking and reasoning, as pointed out by Strauss and Lehtinen.[5] It is felt, however, that the EEG provides a valuable tool in evaluating the

state of health of the individual following the assault of the encephalitis complicating rubella. It is easy for one to be mistaken clinically in one's judgment of persistent emotional instability as a sign of persistent brain damage and vice versa. The EEG provides a more accurate method of arriving at a basis for prognosis when it is used in combination with the careful clinical examination. The fact that persistent EEG changes occur in the otherwise normal individual would force one to maintain a guarded prognosis as to the patient's future ability to adjust to the complexities of life.

The need for close follow-up of these patients on the part of the physician cannot be too strongly emphasized. The early recognition of the child who is developing adjustment problems is essential so that prophylactic measures may be instituted before parental fatigue and social ostracism occur. In reviewing the high incidence of emotional instability, disturbances of concentration, memory defect and hyperactivity, one should consider the problem of when these children are ready to return to school. Considering the fact that such great improvement has been seen during the first year following the onset of the illness, one would be inclined to recommend that these children be given a year's vacation to permit them adequate time for recovery. If earlier return is contemplated it should be done only after careful evaluation of the child.

Of course, there are occasional patients who will eventually require institutionalization. In this group of patients there are three individuals who probably will need this step. This should not be viewed entirely as the final irredeemable stage; for if the child is sent to those institutions especially developed for the rehabilitation of the brain-injured child, a hopeful prognosis for the eventual useful socialization of the individual may still be entertained.[5]

Case Reports

I. Severe residua in the form of subjective changes and severe electroencephalographic changes.

L.S., #105194, was admitted to the Children's Hospital with the complaint of incoherence and marked excitability. Family history and past history were noncontributory. He had become ill 3 days before with the appearance of a rash which became typical of rubella within 24 hr. After 2 days he became drowsy and irritable. Within 24 hr. these symptoms had progressed to severe delirium necessitating hospitalization. Physical examination revealed an acutely ill, delirious, uncontrollable child 7 yr. of age with a fading measles rash. Significant features were widely dilated pupils unresponsive to light, meningeal signs, generalized spasticity with signs of pyramidal tract involvement and absent abdominal reflexes. Lumbar puncture revealed a clear fluid containing 122 lymphocytes/cmm., total protein 86 mg./100 cc. and glucose 61 mg./100 cc.

He remained in a delirious state for 2 days and then slipped into deep coma which persisted for 10 days. There was slight improvement to a semicomatose state during the following 15 days after which he began to attempt to talk. During this period the patient was markedly spastic with severe nuchal rigidity.

The first EEG (Fig. 1a) was taken on the 22nd day after onset of symptoms during the period of semi-coma. This showed a dominant 2-3/sec. slow wave pattern with superimposed fast 25/sec. rate.

From the 6th wk. of his illness, the child began to improve rapidly. He had developed a monotonous tremulous voice with improvement in spasticity. Occasionally he complained of severe hyperesthesia of both legs.

When the next EEG was taken on the 70th hospital day, he showed a spastic paraplegia and ataxia of upper extremities with a fine rapid tremor. Pupils remained widely dilated and unresponsive.

At this time the EEG showed a fast 30/sec. activity superimposed on a varying base line sway. The primary rate was 4-6/sec. Occasionally it was as slow as 1-2/sec. Hyperventilation brought out the 1-2/sec. activity. There was no focus (Fig. 1b).

The patient was discharged on the 75th hospital day. He improved rapidly, regaining muscle control and being able to walk within a few weeks. However, he shortly became a severe behavior problem. The slightest interference with his desires resulted in temper tantrums in which he would

break furniture, strike his mother and scream at the top of his voice. Often he became seriously depressed, saying "I wish I had died." He began to lie about things of little importance. His memory for past events was excellent. Memory for recent occurrences was spotty and undependable. Upon returning to school 8 mo. after onset he had a difficult time due to hyperactivity, inability to concentrate and frequent emotional outbursts.

Physical examination 10½ mo. after onset revealed an apparently normal child with dilated pupils reacting actively to light but sluggishly to accommodation. Tremor was evident only in his handwriting. The outstanding feature of the EEG taken on this occasion was the fast 26/sec. rate which was superimposed on 8-9/sec. activity. Hyperventilation brought out high voltage 5/sec. waves in all leads which persisted after hyperventilation. This record showed less slow high voltage waves and less fast activity than previously (Fig. 1c).

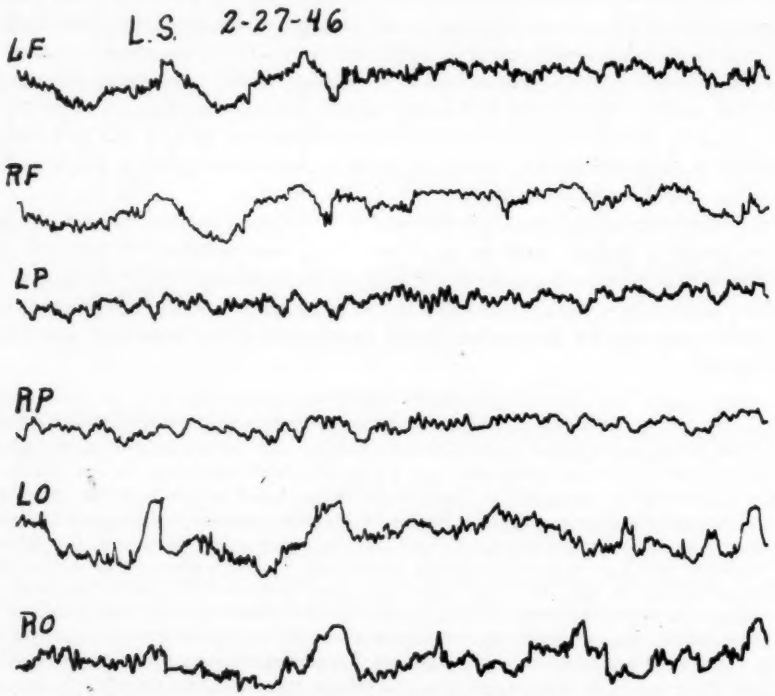

FIG. 1a. 22 days after onset of encephalitic symptoms showing 2-3/sec. slow wave patterns with superimposed 25/sec. activity.

The patient was again seen 2 yr. and 1 mo. after onset. His periods of emotional lability had improved in that weeping spells were less frequent. Temper tantrums were unchanged, and school authorities had suggested that he be suspended due to his uncontrollable behavior and upsetting influence on other pupils. He seemed to be getting worse as a behavior problem. Memory difficulties persisted. Fabrication had continued. He seemed to go out of his way to hurt people's feelings. Ability to concentrate and hyperactivity had improved but remained a disturbing element. Again physical examination was unrevealing except for sluggish pupillary reactions. The dominant rate of the EEG at this time was a low voltage 24-26/sec. activity. Some 9-10/sec. rate was seen in the occipital leads particularly. There was slowing to 6/sec. rate with hyperventilation. The record was still very abnormal, although showing improvement. Some normal alpha activity had begun to appear (Fig. 1d).

II. Severe behavior difficulties and mild electroencephalographic changes.

P.H., #106786, 6 yr. of age, was admitted to the Children's Hospital with the complaint of increasing drowsiness of 24 hr. duration. Family history and past history were noncontributory. He had become ill 1 wk. previously with fever, conjunctivitis and nasal catarrh which had progressed in severity. A typical measles rash appeared on the 4th day. During the 24 hr. preceding admission he had become progressively more drowsy. Physical examination on admission revealed a well developed, well nourished, acutely ill white boy in semi-coma with a fading measles rash. Significant findings were meningeal signs, bilaterally positive Babinski reflex, absent abdominal and hyperactive deep reflexes. Lumbar tap revealed a slightly hazy spinal fluid containing 460 WBC with 90% lymphocytes/cmm., glucose 84 mg./100 cc. and total protein 83 mg./100 cc.

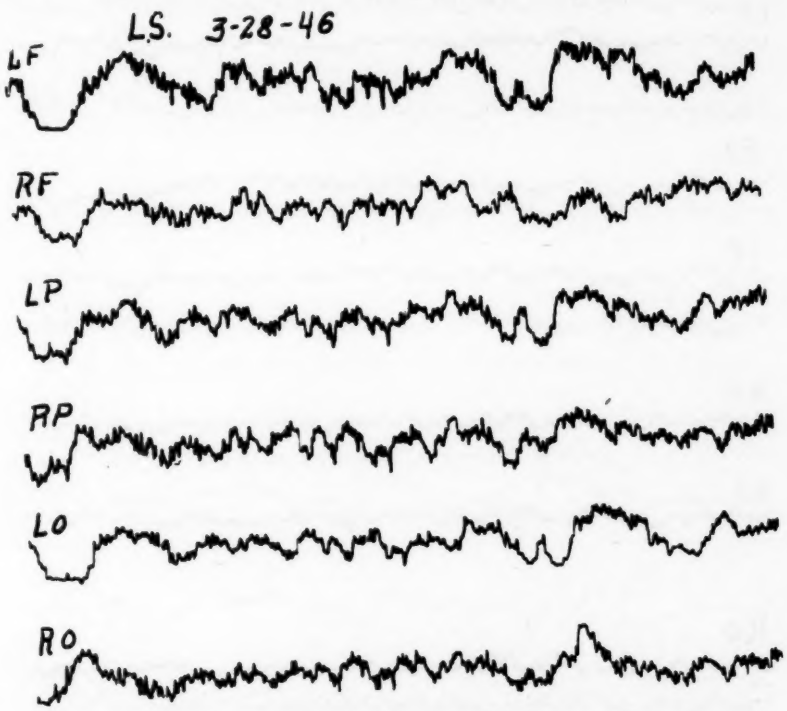

FIG. 1b. 70 days after onset still showing general pattern similar to initial EEG.

Within 24 hr. after admission the child had become comatose and remained in this state for 27 days. Throughout this period his extremities were extremely spastic. He had frequent convulsive twitchings of both arms and right face. Right facial weakness persisted.

The first EEG was taken after he had been in a comatose state for 10 days. All leads showed a rate of 1-2/sec. with persistent depression of voltage and base line sway (Fig. 2a).

The patient slowly improved and by the 40th day of his illness was beginning to attempt to speak. For the next 2 wk. there was marked fluctuation in the state of consciousness. During lucid moments there was considerable improvement in speech but demonstrated constant anomia which was slow to disappear. The spastic paraplegia required 5 mo. of physiotherapy and orthopedic procedures to overcome the severe flexion contractures.

At the time this EEG was taken 5½ mo. after onset, the child was alert, happy and eager to please everyone. However, he was easily upset and cried without provocation. His physical disabilities were a contracture of the right Achilles tendon and marked difficulty in writing. He walked

with a slight limp. All leads of the EEG showed a primary rate of 7/sec. This was interspersed with a low voltage fast 25/sec. rate Hyperventilation brought out high voltage 3-4/sec. waves. This record was markedly improved over the previous ones. The 7/sec. rate was normal for this age (Fig. 2b).

Shortly thereafter he was discharged from the hospital. His emotional instability became intensified at home. At this time it was found that shortly before he had become ill his father deserted the family. No attempt has been made to explain this situation to the child although the child had been closely attached to his father. Temper tantrums became frequent and intense whenever his wishes were blocked. His grandmother lived with the family and failed to accept the fact that the boy was ill. Her attitude has been one of complete intolerance for his behavior.

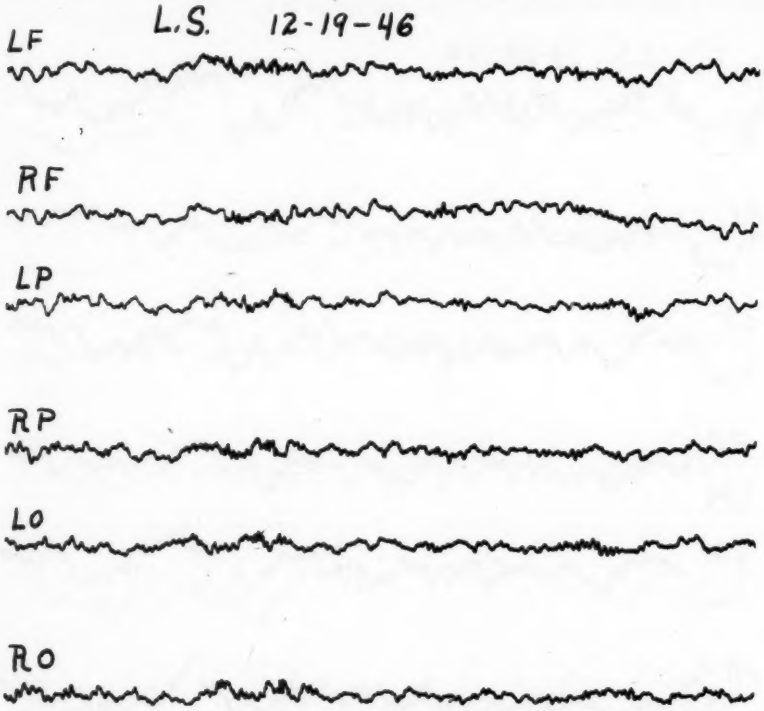

FIG. 1c. 10½ mo. after onset showing improvement but with persistence of 26/sec. rate throughout record.

He returned to school shortly after discharge from the hospital. Considerable difficulty with his work highlighted the entire year of schooling. He had frequent tearful episodes at school, some so severe that he had to be excused from school for the day. His ability to concentrate was poor and hyperactivity further disturbed his work. Difficulty with handwriting added to his disturbances.

A remarkable difference in the child was observed during his 2nd year of school after his illness. Although he had been more and more difficult to handle at home, he was well behaved, quiet, co-operative and happy in school. The mother had little or no control over him. However, his older brother, who had taken over the status of father in the home, could deal with him quite effectively.

It was interesting that the child fabricated constantly at home. His memory was unaffected. He was also able to establish excellent relationships with the neighborhood children.

The child was re-examined 1 yr. and 10 mo. after the onset of symptoms. The only physical defects noticeable were persistent difficulty with handwriting and fatigue of the right leg upon exercise. The EEG taken at this time showed a 7-8/sec. occipital rhythm. Fast activity still persisted in the

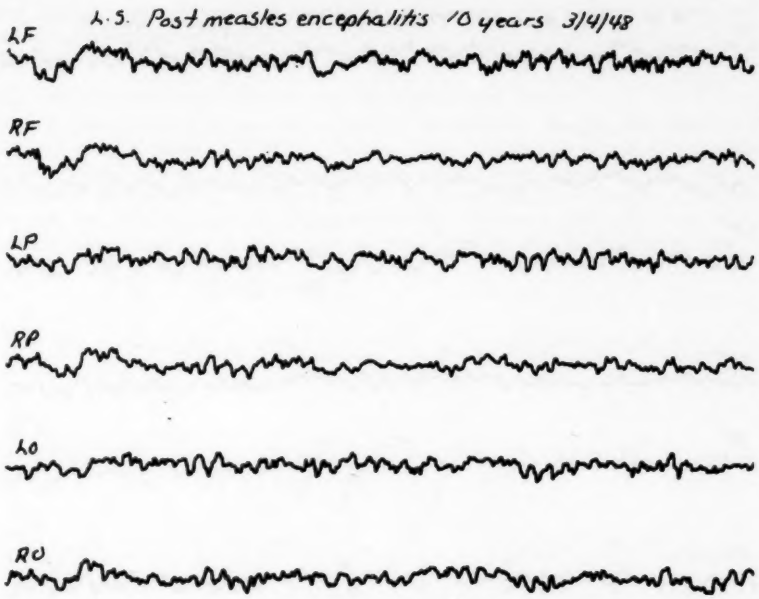

FIG. 1d. 2 yr., 1 mo. after onset, demonstrating persistence of abnormal 24-26/sec. rate.

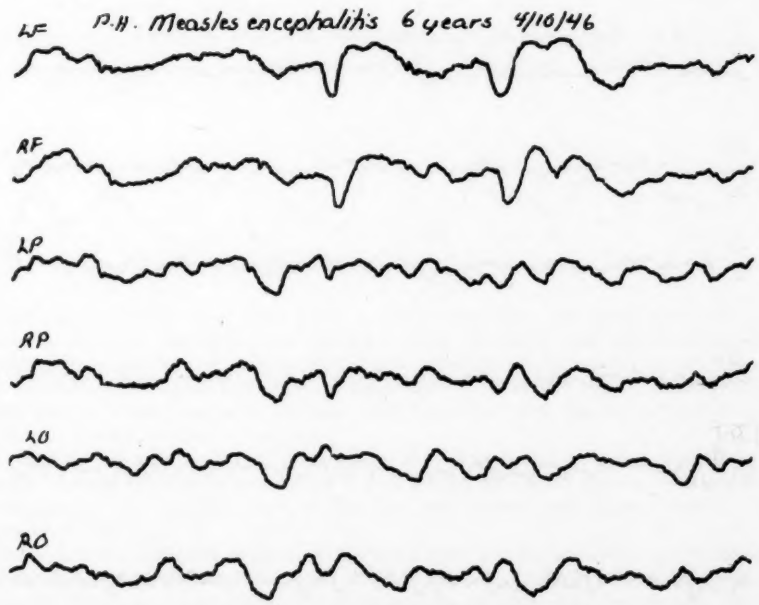

FIG. 2a. 10 days after onset showing grossly abnormal 1-2/sec. rate.

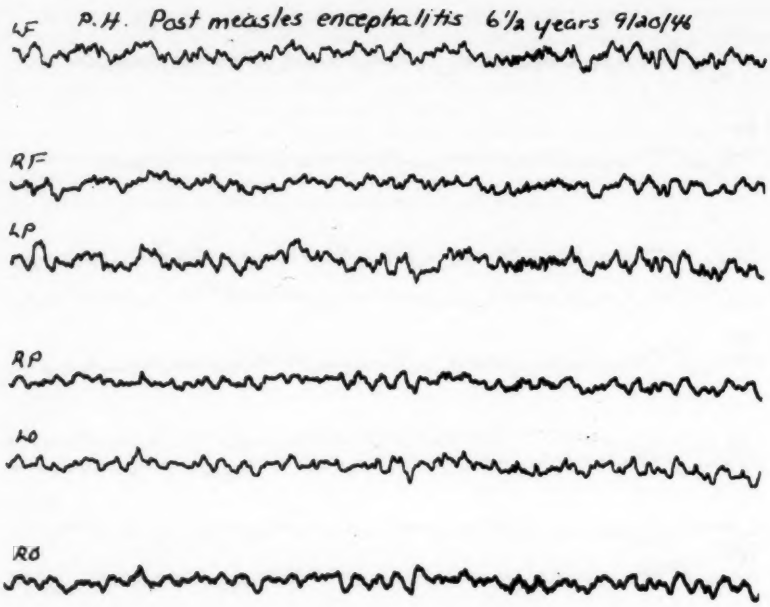

FIG. 2b. 5½ mo. after onset showing considerable improvement with primary rate of 7/sec., interspersed with low voltage 25/sec. rate.

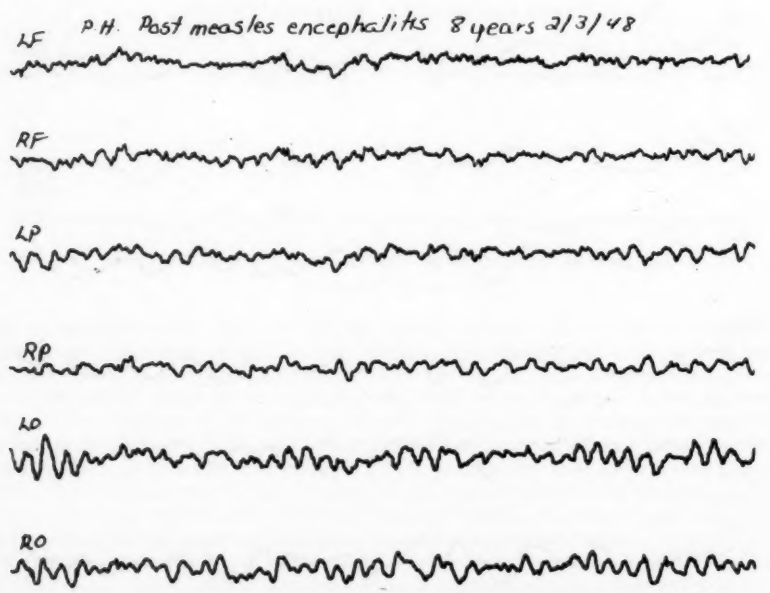

FIG. 2c. 1 yr., 10 mo. after onset showing essentially normal EEG.

frontal leads. Hyperventilation failed to bring out slow activity which was seen 17 mo. ago. The record was essentially normal (Fig. 2c).

One would be loath to attribute all this child's difficulties to organic brain disease.

III. Mild subjective residua and mild electroencephalographic changes.

D.S., #108809, 7½ yr. of age, was admitted to the Children's Hospital with complaint of repeated generalized convulsions of 10 hr. duration. Family history and past history were noncontributory. She had become ill 6 days previously with fever, nasal catarrh and mild cough which progressed in severity. On the 3rd day a typical measles rash appeared. Three days later she had intermittent periods of drowsiness and during the next morning there was the sudden onset of a severe generalized clonic convulsion which continued to recur until admission to the hospital. Examination

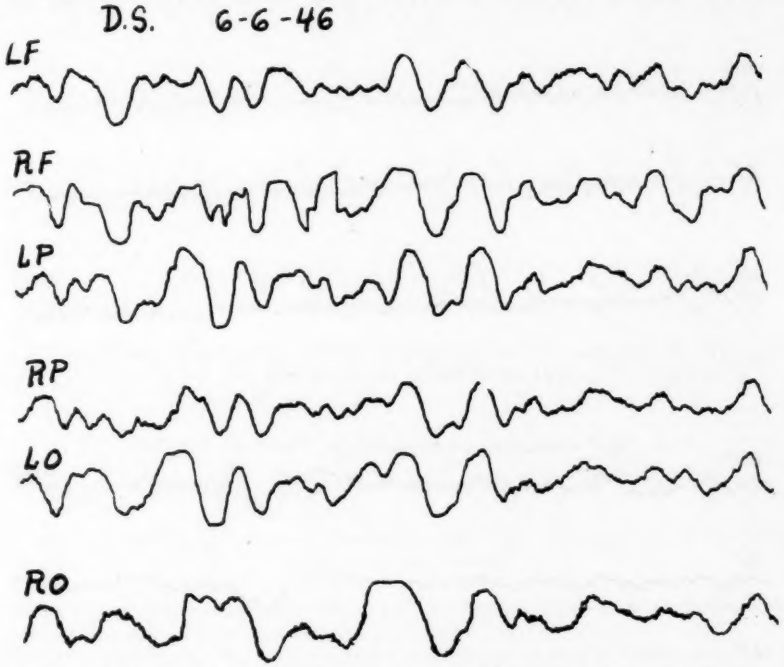

FIG. 3a. 10 days after onset showing persistent 2-3/sec. activity in all leads.

revealed a thin, well developed white girl in a semicomatose state, responding vigorously to mild stimulation. A fading measles eruption covered the body. Meningeal signs and bilaterally positive Babinski reflexes were present. Reflexes in the upper extremities were hyperactive; but abdominal, knee and ankle reflexes were unobtainable. Lumbar tap revealed a clear spinal fluid under pressure of 270 mm. H_2O containing WBC 180/cmm. with lymphocytes 90%, glucose 52 mg./100 cc. and total protein 100 mg./100 cc.

Immediately following removal of 5 cc. of spinal fluid, the patient became rational and fairly well oriented. However, drowsiness persisted for 6 days. By the 6th day all abnormal physical findings had disappeared. The first EEG, taken 10 days after onset, showed persistent high voltage 2-3/sec. activity in all leads (Fig. 3a).

The patient was discharged to her home and re-examined 7 mo. after onset of symptoms. At this time she had difficulty sleeping. After going to bed at night often it was 4 or 5 hr. before the child fell asleep. Her memory was unaffected. Physical examination revealed no abnormalities. The EEG showed a dominant rate of 9/sec. There was an 18-20/sec. rate interspersed. Hyperventilation brought

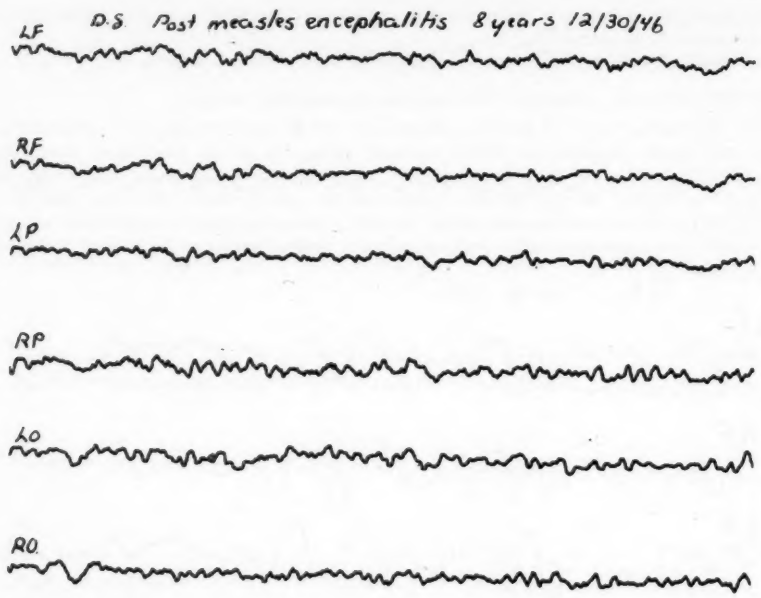

FIG. 3b. 7 mo. after onset showing great improvement with dominant rate of 9/sec. and 18-20/sec. rate interspersed.

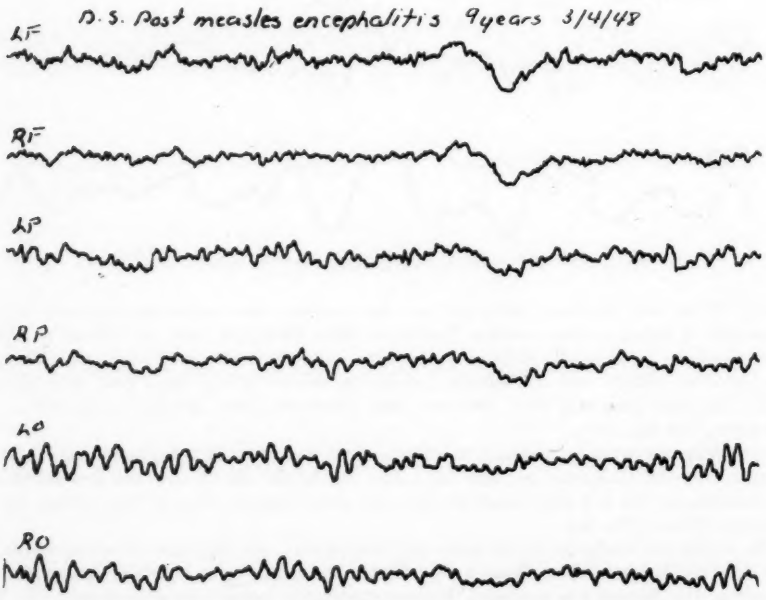

FIG. 3c. 1 yr., 9 mo. after onset showing practically normal record in resting state.

out some high voltage 3-4/sec. waves. The record was greatly improved over the previous record (Fig. 3b).

The child was again seen 1 yr. and 9 mo. after the onset of her illness. By this time hyperactivity and disturbance of concentration had disappeared. She was getting excellent grades in school, although it was difficult for her to grasp new concepts. Her sleep disturbance persisted but was much less severe. Only occasional episodes of emotional instability occurred. She had never represented any difficulties with behavior. It was interesting, however, that the child had developed obsessive-compulsive tendencies toward her school work. She would not attend school unless she

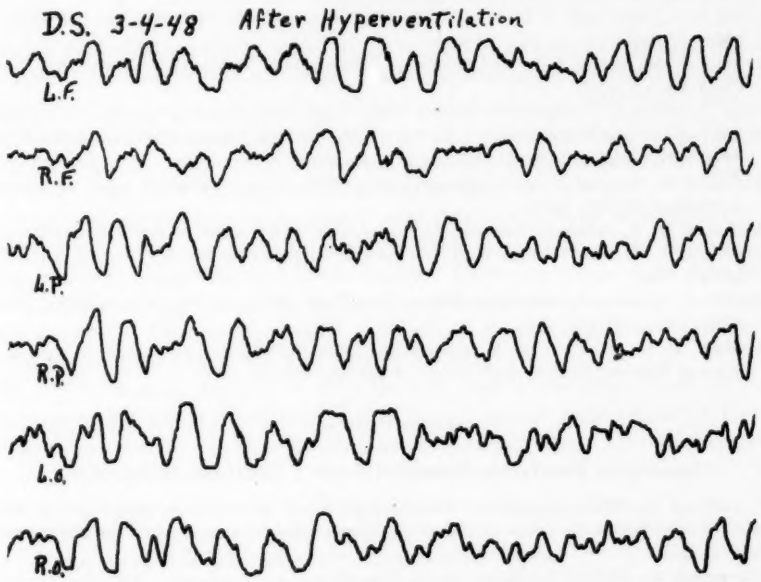

FIG. 3d. Upon hyperventilation, remarkable electric instability is demonstrated with high voltage 3-4/sec. waves in all leads.

had completed her homework and understood it perfectly. She was frightened by the introduction of new subjects because she was not sure she could do the work.

This EEG, taken 21 mo. after onset, revealed a dominant rate of 9-10/sec. with low voltage fast activity superimposed and interspersed. There was slightly higher voltage on the left. Hyperventilation brought out high voltage 3-4/sec. waves. This record showed more normal activity in the resting record (See Figs. 3c and d).

SUMMARY

The acute symptoms of onset of 31 cases of rubella complicated by encephalitis are presented. The correlation of the incidence of severe residua with the slow recovery from acute symptoms is pointed out.

The residual symptoms developing in 12 patients followed over a period of two years are described. It is emphasized that disturbances of personality, concentration and memory are most frequent in occurrence. The electroencephalographic changes occurring in these patients are described and a correlation between the clinical severity of residua and electroencephalographic changes is presented.

The need for close follow-up of the convalescing postencephalitic patient is stressed so that developing behavior difficulties may be recognized and intelligently managed. The

value of the EEG in the evaluation of the difficulties of the postencephalitic patient is discussed.

Selected case reports are presented demonstrating the electroencephalographic changes and the associated clinical manifestations.

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SPANISH ABSTRACT

Sarampion Encefalitis: Estudio Clínico y Electroencefalográfico

Se presentan los sínotomas agudos del comienzo de 31 casos de rubéola complicada por encefalitis. Se demuestra la correlación de la incidencia de severos residuos con el lento restablecimiento de síntomas agudos.

Se describen los síntomas residuales que se desarrollaron en 12 pacientes observados durante un período de dos años. Se hace notar que el desorden de personalidad, concentración y memoria es lo que más frecuentemente ocurre. Se describen los cambios electroencefalográficos que ocurrieron en estos pacientes y se presenta una correlación entre la severidad clínica de residuos y los cambios electroencefalográficos.

Se acentúa la necesidad de seguir muy de cerca al paciente postencefalítico convalesciente de manera que se puedan reconocer dificultades de comportamiento y se puedan manejar inteligentemente. Se discute el valor del EEG en la avaluación de las dificultades del paciente postencefalítico.

Se presentan reportes de casos seleccionados demostrando los cambios electroencefalográficos y las manifestaciones clínicas asociadas.

102 Alleghany Avenue, Towson, Baltimore

STAPHYLOCOCCUS AUREUS IN AN OUTBREAK OF INFANTILE DIARRHEA

By HARVEY B. LYON, JR., M.D., AND LOWELL A. RANTZ, M.D.
San Francisco

INFANTILE diarrhea may be caused by one or more of a variety of organisms including viruses.[1] One such organism, Staph. aureus, is well known for its ability to cause acute, short-lived episodes of nausea, vomiting and diarrhea. A soluble enterotoxin has been implicated. Several investigators[2-4] have reported epidemics of infantile diarrhea in which this organism was cultured from some of the stools, while at the same time it was being found much less frequently in nondiarrheal stools.

The purpose of this paper is to report in some detail an outbreak of infantile diarrhea in which Staph. aureus was recovered from the stools in nearly all of the cases.

The epidemic began suddenly in the Stanford University Hospitals Nursery which consists of four separate rooms for full term newborn infants and one large room for premature infants. This incident was limited to two of the full term nurseries. The essential clinical and bacteriologic details are presented in Chart 1.

The first loose stools appeared at about the same time in two infants in Room No. 1. Bilateral conjunctivitis appeared shortly after birth in one of these infants. A bacterial etiology of this disease was not established since only a few Staph. aureus albus were recovered from the discharge. Both of these infants were dismissed without stool cultures or medication but it is known that diarrhea did not continue at home. The third infant to be affected in this room entered during the early phase of the epidemic and was the last to develop signs of infection, about 24 hours after the others.

Nine out of 10 newborn infants in Room No. 2 developed loose stools within a 10 hour period. The only exception entered the room four hours before the first diarrheal stool was noted and did not receive anything by mouth until 12 hours after entry. A water feeding was then given. Two hours later this infant was transferred to an observation room. The most recent dismissal prior to the outbreak was four hours before its onset. This child had a formula feeding two hours before leaving the hospital and remained well. Thus the contamination causing the epidemic might have occurred during the feeding following dismissal of this child.

Manifestations of the disease were limited to loose, greenish stools occurring 4 to 10 times a day and persisting over periods of from 30 to 84 hours. No vomiting or fever developed and no signs of dehydration were noted. Close observation of the skin, ears, nose, throat and lungs revealed no signs of infection at any time.

Isolation precautions were instituted shortly after the first diarrheal stools appeared. One doctor and one nurse were assigned to the rooms involved and aseptic technic was carefully practiced.

Staph. aureus was recovered in large numbers from stools obtained from seven of the

From the Departments of Pediatrics and Medicine, Stanford University School of Medicine, San Francisco, Calif.

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nine patients and cultured directly on blood agar plates at the onset of diarrhea. The organism in every instance formed coagulase. One of two specimens devoid of staphylococci contained a heavy growth of P. vulgaris which may have interfered with the growth or isolation of any staphylococci present; in the other case there was a heavy growth of nonhemolytic enterococci. Throat cultures of one of the infants whose stool contained a heavy growth of staphylococci revealed many of the same organisms. This organism was not isolated from the nasopharynges of the other eight infants.

Dietary treatment was started after the initial cultures had been obtained. Water was

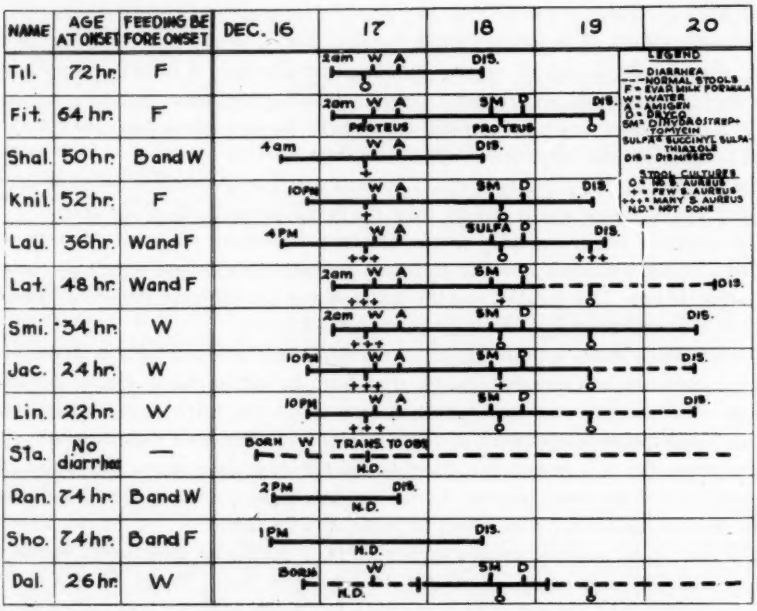

CHART 1. Clinical Course and Results of Bacteriologic Study in 13 Cases of Probable Staph. Aureus Diarrhea in Newborn Infants

given by mouth every three hours for the first eight hours. An oral amigen-electrolyte mixture was then administered for a 28 hour period and was followed by a dryco® formula without sugar.

Chemotherapy was begun when the bacteriologic findings were reported. Four of the infants had been dismissed from the nursery during the preceding 24 hours and thus were not treated with antibacterial agents. Seven of the remaining eight infants received dihydrostreptomycin in a dosage of 0.1 gm. every four hours mixed in bottle feedings. One infant received sulfasuxidine 1.0 gm. every four hours in the same way.

Eight stools were cultured two hours after starting medication. No staphylococci were isolated from six. Two, obtained from infants who were receiving dihydrostreptomycin, showed a light growth of this organism. On the next day, after 26 hours of medication, one of seven stool cultures was positive for Staph. aureus. This patient was the one receiving sulfasuxidine. He was dismissed on the same day without further cultures or treatment, but no diarrhea was reported at home. All seven throat cultures were negative

at this time. Five patients remained in the hospital on the fifth day. All cultures were negative for staphylococci and all stools were normal in appearance. None of the patients exhibited diarrhea after leaving the hospital according to reports from attending physicians.

The nursery staff was studied for the purpose of discovering a possible source of the epidemic. Evidence of infection by staphylococci was not obtained in any of the personnel, nor were these organisms isolated from the materials obtained from the nose and throat of the four nurses who were immediately responsible for the care of the infants before the outbreak began.

Discussion

Staph. aureus has been recognized for many years as a cause of acute gastroenteritis. Nausea, vomiting and diarrhea following shortly after the ingestion of food contaminated by this organism occurs frequently. A soluble enterotoxin, which is formed by certain strains of staphylococci, is the immediate cause of the gastrointestinal disturbance. Growth of the organism in the gastrointestinal tract is not necessary and its recovery from the stool is rarely accomplished.

True infectious diarrhea caused by Staph. aureus in the newborn infant has been reported.[2-4] In these cases large numbers of this organism were present in the fecal flora. The epidemic described in these reports was of this type.

Staphylococci were recovered, usually in large numbers, from the stools of seven of nine infants affected. Technical difficulties may have prevented the isolation of this organism in one additional case. This high rate of recovery from diarrheal stools strongly suggests that Staph. aureus was the etiologic agent of the disease. A control study not reported here in detail was conducted in which serial stool cultures were obtained in 20 healthy babies. Staph. aureus was recovered on only one occasion by direct inoculation of feces on blood agar plates, demonstrating that this organism is rarely present in the normal fecal flora of infants.

The disease itself was mild. Dehydration and disturbances of electrolyte balance did not occur. The diarrhea ran its course in two to three days. Treatment with dihydrostreptomycin was instituted. This drug was used because recent reports[5,6] indicate that hospital infection by staphylococcus is likely to be caused by organisms highly resistant to the action of penicillin. Such strains are regularly inhibited *in vitro* by streptomycin. Administration of the drug was associated with a prompt disappearance of staphylococci from the stools. The effect of this therapy could not be evaluated since the disease was self-limited. Patients who did not receive antimicrobial therapy did not have a more prolonged course or more severe illness.

Summary

An outbreak of infantile diarrhea in newborn infants, caused probably by Staph. aureus, is described. The disease was short-lived, mild and self-limited.

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SPANISH ABSTRACT

Estafilococo Aureus en un Ataque de Diarrea Infantil

Se ha reportado diarrea verdaderamente infecciosa causada por estafilococo aureus en el infante recién nacido. En estos casos grandes números de este organismo estaban presentes en la flora fecal. La epidemia descrita en este papel fué de este tipo.

Los estafilococos fueron recogidos, generalmente en gran número, de las deposiciones de 7 de 9 infantes afectados. Las dificultades técnicas pueden haber prevenido el aislamiento de este organismo en un caso adicional. Esta alta proporción de recobro de las deposiciones de diarrea fuertemente sugieren que los estafilococos aureus fueron el agente etiológico de la enfermedad. Se condujo un estudio de control que no es reportado aquí en detalle, en el cual cultivos de deposiciones en series fueron obtenidos de 20 bebés sanos. Estafilococo aureus fué recobrado en solamente una occasión por inoculación directa de excrementos en vidrios planos agar de sangre, demostrando que este organismo está rara vez presente en la flora fecal normal de infantes.

La enfermedad misma fué suave. No ocurrieron deshidratación ni desordenes de balance electrólito. La diarrea siguió su curso en 2 a 3 días. El tratamiento con dihidrostreptomicina fué instituído. Esta droga fué usada porque informes recientes indican que infección de hospital por estafilococo es probable que sea causada por organismos altamente resistentes a la acción de la penicilina. Tales cepas son regularmente inhibidas en vitro por la estreptomicina. La administración de la droga fué asociada con el pronto desaparecimiento de los estafilococos de las deposiciones. El efecto de esta terapia no puede avaluado ya que la enfermedad se limita por si misma. Los pacientes que no recibieron terapia antimicrobiana no tuvieron una enfermedad de curso más prolongado o más severa.

Clay and Webster Streets

POSTPRANDIAL LIPEMIC RESPONSE IN INFANTS AND CHILDREN

By W. Robert Elghammer, M.D., John M. Reichert, M. D., and Herbert F. Philipsborn, Jr., M.D.
Chicago

IT HAS been observed, probably for centuries, that blood drawn after the ingestion of fatty foods has a milky opalescent character. In 1877 Edmonds[1] reported the first description of blood observed under the dark-field microscope and since then various investigators have noted minute, freely spinning particles. It was suggested that these particles may be protein (Raehlmann),[2] fat (Neumann),[3] fragmented leukocytes or tiny parasites (Kahane).[4]

Gage and Fish,[5] in 1924, termed these bodies chylomicrons, as they believed them to be composed of fat, and estimated their diameter to be one micron. They also recorded the postprandial rise and fall in the number of these particles.

Several years later, Frazer and Stewart[6] determined that the chylomicrons were neutral fat and bore no relation to blood cholesterol, phospholipids or proteins. Schroeder and Holt[7] found that the chylomicron counts of infants varied in direct proportion to the fat content of the formula which was given.

Great quantitative variations of the fatty constituents of the blood may occur in the same individual under apparently[8] identical conditions. This is to be expected when one considers that the amount of fat present in the blood at any moment represents an equilibrium between factors affecting the rate of absorption and those determining the rates of utilization and deposition. The digestion and absorption of fat depends, in part, upon the amount and activity of the various lipases, the pH of the intestinal contents, the presence of bile, the degree of intestinal motility and the effectiveness of the phosphorylation mechanism.[9] The role of intestinal motility is more important than is usually recognized. Roentgenographic studies reported by Snell and Camp[10] have demonstrated both hypotonicity and hypomotility of the small intestine in patients having chronic intestinal indigestion. The increased intestinal motility following the administration of neostigmine (prostigmine®) or cascara to patients with fibrocystic disease of the pancreas was reported by Flax et al.[11] to be accompanied by an increase in the serum vitamin A content. Wade[12] has reported marked clinical improvement in patients with celiac disease following the injection of posterior pituitary extract.

Despite the many factors affecting fat absorption, the vitamin A absorption curve, as employed by Chesney and McCoord[13] and May and McCreary,[14] has proved a valuable aid in the study of both fibrocystic and celiac diseases. The disadvantages of the vitamin A curve are that it requires repeated venipuncture and the withdrawal of relatively large amounts of blood. Furthermore, the laboratory procedure is rather difficult and requires a skilled technician.

From the Children's Memorial Hospital, Chicago, Ill.
Aided by a grant from Mr. and Mrs. Rossell Packard.
Read before the Chicago Pediatric Society, May 14, 1949.
(Received for publication Aug. 2, 1949.)

The preceding studies of chylomicrons and fat metabolism led us to a simple test comparable in clinical value to the more complicated vitamin A absorption test. This test, which will be described, is an application of the chylomicrograph. It requires only a few drops of blood, is a rapid and simple procedure and can be done wherever facilities for dark-field microscopy exist.

Methods

Subjects: All were patients in the Children's Memorial Hospital and ranged in age from 6 wk. to 3 yr. Group 1 consisted of 22 infants and children with normally functioning gastrointestinal tracts as evidenced by good nutrition, normal weight gain and normal stools. These patients were convalescing from acute infections or surgical procedures. Group 2 consisted of 10 infants and children with abnormally functioning gastrointestinal tracts and included 8 patients with fibrocystic disease, 1 with celiac disease and 1 with megacolon. The diagnoses of the patients were made in accordance with the generally accepted criteria for the disease as stated by Andersen[15,16] and Hirschsprung.[17]

Technics: The patients were fasted 12 to 15 hr. before being tested; small infants were fasted for only 8 to 10 hr. The test meal consisted of cream, 30 cc./kg. body weight with a maximum of 120 cc., and was given by cup or gavage. No other foods or liquids were allowed until the test was completed. Capillary blood specimens were obtained by finger-puncture at hourly intervals, the drop placed on a clean glass slide and covered with a cover slip. Light manual pressure was applied so as to distribute a thin film of blood under the entire cover slip. The slides were examined under the dark-field microscope, using the oil immersion lens, within 1 hr. after preparation. A transparent film, onto which a 1 mm. square had been ruled, was fitted into the ocular end of the microscope. The chylomicrons appear as small refractile bodies with Brownian movement. The numbers appearing in the ruled

TABLE I

Patients with Normal Digestive Tracts*

Case No.	Chylomicron Count				
	Fasting	1 hr.	2 hr.	3 hr.	4 hr.
1	1.8	13.3	6.0	9.4	1.5
2	1.5	2.8	4.8	10.1	9.8
3	2.0	3.1	4.5	7.2	8.0
4	1.1	2.8	6.5	3.7	4.7
5	1.1	3.2	5.9	12.0	16.8
6	1.3	0.7	10.6	11.6	4.2
7	0.8	—	3.9	7.0	9.0
8	0.8	—	0.6	0.6	8.1
9	1.2	1.7	3.8	6.8	8.5
10	0.5	1.9	11.0	6.2	7.2
11	0.4	1.0	4.1	8.1	4.3
12	1.1	—	10.1	8.2	5.7
13	1.0	—	9.9	9.6	5.4
14	1.1	2.7	7.6	10.2	2.8
15	0.9	4.9	13.3	17.9	13.6
16	1.0	2.5	6.6	4.7	4.7
17	1.1	1.4	4.8	15.3	7.8
18	1.5	3.7	14.1	10.0	4.6
19	0.6	0.9	2.6	3.7	9.2
20	1.9	3.8	5.8	10.3	6.5
21	1.3	9.7	16.7	10.7	9.1
22	1.4	7.4	5.7	9.5	6.7
Average	1.1	3.7	7.8	8.7	6.2
Median	1.1	2.8	5.8	9.4	6.7

* As evidenced by good nutrition, normal weight gain and normal stools.

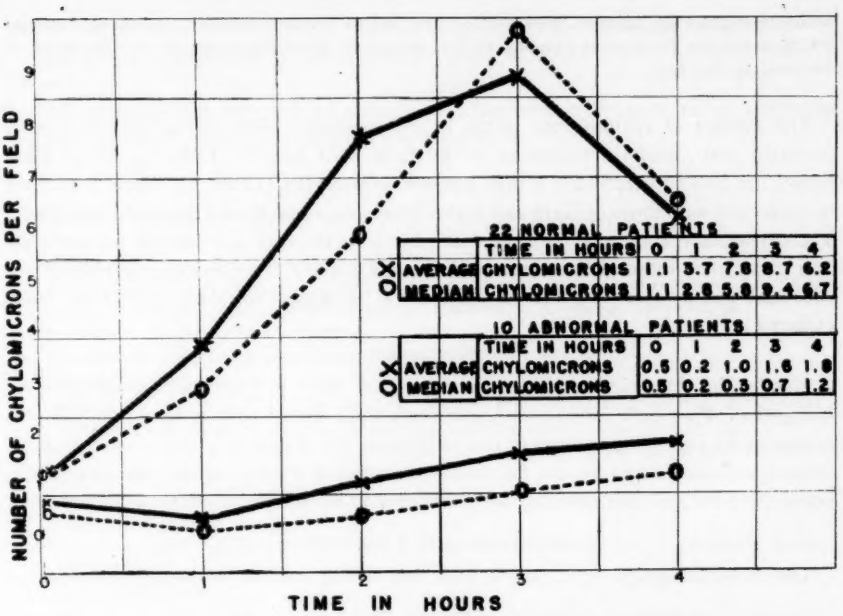
NUMBER OF CHYLOMICRONS PER FIELD
TIME IN HOURS
22 NORMAL PATIENTS
TIME IN HOURS 0 1 2 3 4
AVERAGE CHYLOMICRONS 1.1 3.7 7.8 8.7 6.2
MEDIAN CHYLOMICRONS 1.1 2.8 5.8 9.4 6.7
10 ABNORMAL PATIENTS
TIME IN HOURS 0 1 2 3 4
AVERAGE CHYLOMICRONS 0.5 0.2 1.0 1.6 1.8
MEDIAN CHYLOMICRONS 0.5 0.2 0.3 0.7 1.2

CHART 1. Chylomicrographs of normal and abnormal groups tested.

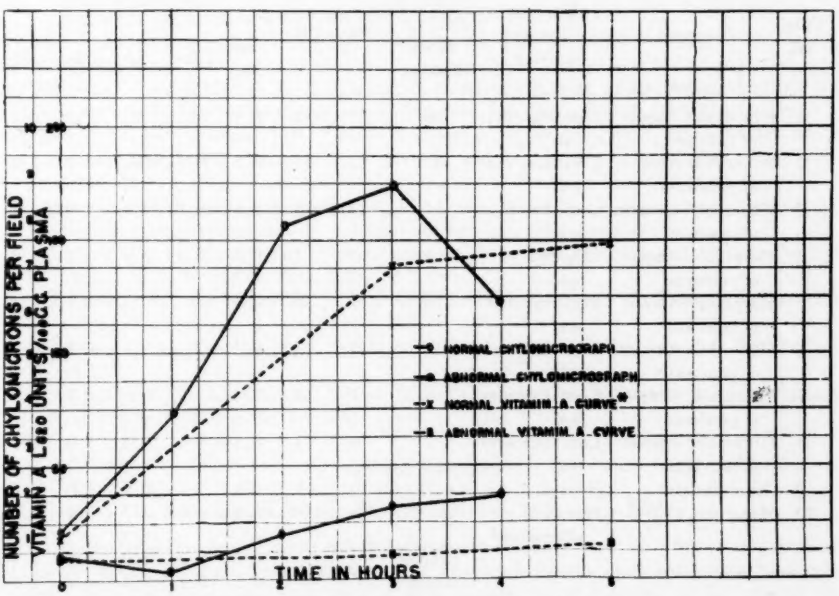

CHART 2. Graphic comparison of averages of chylomicrographs and vitamin A curves of normal and abnormal groups tested.

* Average of vitamin A curves of 30 normal patients, in same age group as those of this study, who were previously tested.

square throughout 20 different fields were counted and an average calculated. It is most important not to change the focus while counting as the plane of the focus constitutes the 3rd dimension of the counting chamber.

Results

The number of chylomicrons in the hourly specimens from normal patients rapidly increased and reached a maximum in the three hour sample (Table I). When these figures are plotted graphically a high peaked curve results (Chart 1). These results are in agreement with those of Gage and Fish,[5] Frazer and Stewart[6] and Schroeder and Holt.[7] The chylomicron counts of the abnormal subjects were lower and showed less variation as a group than those of the normal children (Table II). The chylomicrographs of the abnormal group were low flat curves with a maximum elevation after four hours (Chart 1).

Discussion

Neither the chylomicrograph nor the vitamin A curve is a specific test for intestinal indigestion. They both indicate the momentary lipid level which is the resultant of the factors of fat ingestion, absorption and utilization. The degree of positive correlation between the chylomicrographs and the vitamin A curves of the normal and abnormal groups tested (Chart 2) is such that they are considered to be of equal clinical significance.

Summary and Conclusion

The chylomicrograph is a simple and time-saving method of serially determining

TABLE II

Case No.	Diagnosis	Duodenal Trypsin† Amylase‡	Vitamin A* Determination Fasting	3 Hr.	5 Hr.	Chylomicron Count				
						Fasting	1 Hr.	2 Hr.	3 Hr.	4 Hr.
1	Fibrocystic disease of pancreas	Less than normal	10	25	34	0.1	0	0	0.5	0.4
2	Fibrocystic disease of pancreas	Less than normal	12	12	13	0.6	0.5	0.2	2.2	1.2
3	Fibrocystic disease of pancreas	Less than normal	17	22	28	0.8	0.1	4.7	4.9	2.1
4	Fibrocystic disease of pancreas	Less than normal	3	4	3	0.5	0.3	0.9	0.2	1.8
5	Fibrocystic disease of pancreas	Less than normal	6	7	10	0.9	—	0.3	0.7	3.4
6	Fibrocystic disease of pancreas	Less than normal	10	10	13	0.4	—	0.1	0.7	0.5
7	Fibrocystic disease of pancreas	Less than normal	6	7	10	0.4	—	0.1	0.7	0.3
8	Fibrocystic disease of pancreas	Less than normal	2	4	3	0.5	—	0.6	1.0	0.5
9	Celiac disease	Normal	7	10	9	0.4	—	0.9	2.0	3.2
10	Megacolon	Not determined	—	—	—	0.8	—	2.3	3.4	4.6
			Average			0.5	0.2	1.0	1.6	1.8
			Median			0.5	0.2	0.3	0.7	1.2

* Chesney and McCoord.[13]

† Northrup and Kunitz[18] modification of the method of McClure, Wetmore and Reynolds.[19]

‡ McClure, Wetmore and Reynolds[19] and Philipsborn et al.[20]

neutral blood lipid levels. It is of value in studying chronic intestinal indigestion.

The clinical significance of the chylomicrograph is equal to that of the vitamin A curve.

The advantages of the chylomicrograph over the vitamin A curve are its simplicity, rapidity, availability and use of capillary blood specimens.

ACKNOWLEDGMENT

Valuable technical assistance was given by Miss Helen Cheney.

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SPANISH ABSTRACT

Respuesta Lipémica Postprandial en Infantes y Niños

El quilomicrógrafo es un simple método economizador de tiempo para determinar por series cantidades lípidas de sangre neutral. Es de valor al estudiar indigestión intestinal crónica. La significancia clínica del quilomicrógrafo es igual a la de la curva de la Vitamina A. Las ventajas del quilomicrógrafo sobre la curva de Vitamina A son su simplicidad, rapidez, disponibilidad y uso de muestras de sangre capilar.

114 10½ Street, S.E., Rochester, Minn.

CLINICAL CORRELATES OF THE FAST AND THE SLOW SPIKE-WAVE ELECTROENCEPHALOGRAM

By WILLIAM G. LENNOX, M.D., AND JEAN P. DAVIS, M.D.
Boston

CHILDREN with convulsions or epilepsy constitute a major difficulty for the pediatrician. The problems encountered are greater in children than in adults; the disorder is more common, the causes more serious and more diverse, the seizures more frequent and variable, the prognosis more uncertain. In partial compensation, the electroencephalogram (EEG) is more revealing in children. What the clinician says to his epileptic patient depends in part on what the brain waves say—hence, the importance of interpretations of the EEG based on broad experience. The alternate dart and dome formation is the most distinctive and informative of the abnormalities associated with epilepsy.

This pattern that recurs at the rate of approximately three per second during petit mal was first described by F. A. Gibbs, H. Davis and W. G. Lennox[1] in 1935. Four years later, Gibbs, Gibbs and Lennox[2] reported a slower version. This was a blunt spike, followed by a slow hump, the pair recurring at a rate of approximately two per second. The authors termed this a "petit mal variant." They pointed out its relative unresponsiveness to changes in the concentration of glucose, oxygen or carbon dioxide in the blood. Alterations that dramatically increased or decreased the three per second dart and dome discharges had little effect on the slower type. Furthermore, this slow formation seemed to be associated with pathology of the brain.

Little further attention has been paid to the slow spike and wave discharge, perhaps because it has not been associated with discrete, stereotyped and easily recognized clinical phenomena and because relatively little has been published on the electroencephalography of young children. It has been pointed out[3] that the EEGs of children subject to astatic or inhibition seizures most often displayed slow spike and wave formations and, also, that this form of seizure was most likely to respond to 3,5,5-trimethyloxazolidine-2,4-dione (tridione®). Injury of the brain of the adult is accompanied by sharp spikes, usually negative or diphasic, but rarely by an alternate spike and wave.

The slow formation is encountered most often in the very young patient. The dominant frequency of the EEG is much slower in the first few years of life than later. Logically, therefore, the slow spike and wave formation might represent simply an immature or young variety of the faster form. If so, patients who have the two per second spike and wave in their EEGs should, as they get older, display the three per second variety. The authors have not as yet observed this transition; rather, the two types seem to remain fairly constant, even when a patient has a record displaying both varieties.

In order to explore the problem presented by electroencephalographic patterns so alike

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From the Children's Medical Center, Boston.

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in form, but so different in speed and in their clinical correlates, a study was made of 400 patients who displayed one or the other of these patterns of abnormal discharge.

Terminology and Methods

"Petit mal" is a vagabond term meaning usually a mild or brief seizure of any sort. We would limit its meaning to embrace a petit mal quartette.

The first and most common member of this quartette is what the French descriptively term "absence." As double identification, we would name it "petite absence"; a 5 to 30 sec. period in which aura, loss of consciousness, movements (except for rhythmic minor twitchings) and sequelae are all absent. Such absences usually recur daily, often many times a day, and tend to disappear along with youth. A synonym is pykno-epilepsy.

The 2nd member of the petit mal quartette is termed "astatic" (or "inhibition") epilepsy; an abrupt loss of postural control with nodding of the head, salaam motions of the trunk, or a limp collapse and fall of the body.

The 3rd member is the familiar, sudden, lightning-like "myoclonic jerk" or flexion of the arms.

The 4th member, "massive myoclonic jerk," is a generalized quick contraction of muscles with jackknifing of the body. These diverse manifestations have in common the alternate spike-wave EEG.

The group of patients with the 3/sec. spike-wave pattern will be termed "fast" and those with the 2/sec. "slow." "Spike-wave" is a general term that includes "fast" and "slow." A more descriptive term for the fast 3/sec. couplet is "dart-dome." The slow 2/sec. couplet could be described as "blunt spike and hump." Periods of amnesia are termed psychic or psychomotor seizures or, if attended by automatic activity, automatisms.

Patients were those seen at the Children's Medical Center. Electroencephalograms were made with a Grass recorder equipped for the most part with 6 or 8 ink-writing pens. Monopolar recording was used throughout.

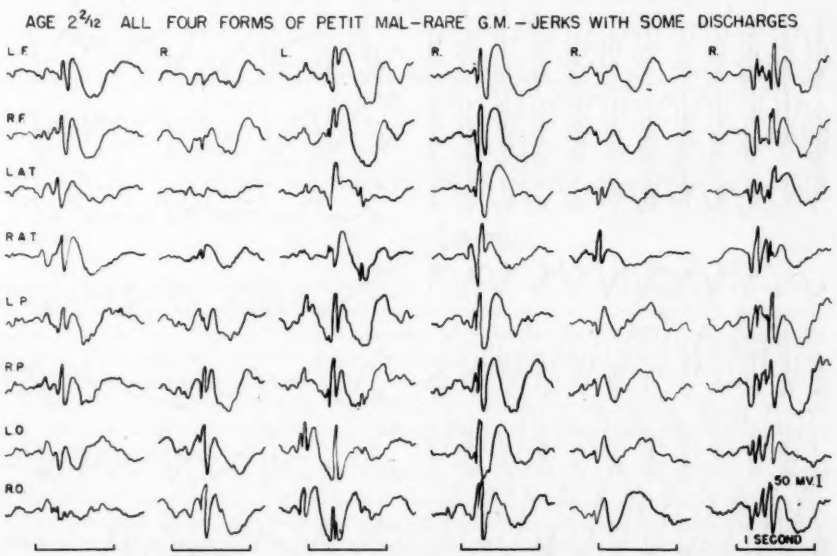

FIG. 1. Sample discharges from EEG of L. V. showing different patterns and different distributions of slow spike and wave discharges in various leads. (In figs. 1 to 9 and 15, the lead is indicated by letters at left. LF and RF stand for L. and R. frontal; LAT and RAT for L. and R. anterior temporal; LT and RT for L. and R. temporal; LP and RP for L. and R. parietal; LO and RO for L. and R. occipital. Horizontal lines represent 1.0 sec.; perpendicular line represents signal made by 50 or 100 mv. In some figures, signal is missing.)

Descriptive

The verbal description of patterns must be supplemented by study of the figures that follow, designed to illustrate both "typical" patterns and variations of the "petit mal variant." The characteristic common to both forms is an alternation of fast and slow waves of high voltage. The slow couplets recur at intervals of from 1 to 2½/sec.; the fast at from 2½ to 4/sec.

The spike and the wave may not have the same rate of recurrence, as is shown when a spike progressively mounts a wave. The configuration of the complex is as important as its rate. The spike characteristically has a duration of 1/15 sec. or longer, the peak is blunt or rounded, and the amplitude often greater than the wave. It may be negative (upward pointing) or diphasic. In an impure or hybrid couplet, the spike is sharp instead of blunt, sometimes as sharp and as tall as the spike of the fast variety, but usually a sharp spike is also short.

The contour of the slow wave or hump (characteristically smooth and rounded in the dart-dome variety) may be somewhat irregular with a sharp downward slope of the curve. In young children, patterns tend to be less typical, the spikes less frequent, the waves slower and their amplitude in relation to the background voltage greater than in older persons. The complex may be as slow as 1/sec. and the voltage of waves as great as 2,000 microvolts (mv.).

When the slow discharge appears simultaneously in all leads, it assumes a variety of forms; characteristic in a frontal lead, it may be only a spike (negative or diphasic) in another lead or only a wave in still another. Examples of such variations in a single recording appear in Figure 1. Because of its elusive and protean characteristics, the slow pattern is studied best with an 8-channel recorder.

A prime difference in the slow and fast discharges is the focal nature of the former—its appearance in only one lead, or in the leads from one side of the brain. The localization may be constant or shifting. The former suggests an underlying neuropathology.

Spike-wave discharges, whether slow or fast, may appear as a short burst lasting only 1 or 2 sec.,

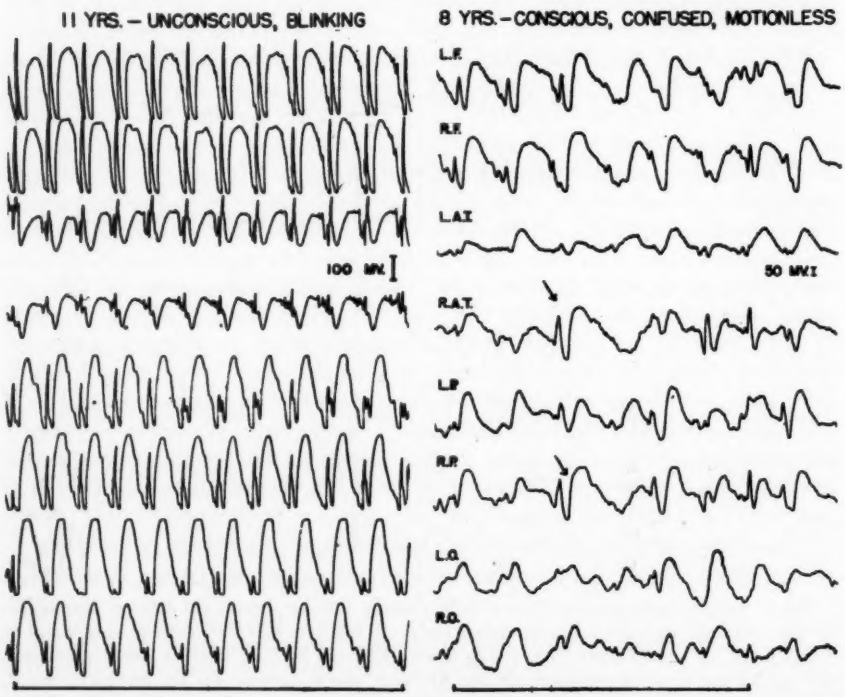

FIG. 2. Comparison of 3/sec. and 2/sec. spike-wave tracings made during minor seizures of Patients K. McN. and M. McI.

or they may form a continuous chain lasting many seconds or even minutes. However, 2/sec. discharges are less gregarious than the 3/sec. The slow spike-wave is more often solitary and chains are more often discontinuous. Solitary discharges may appear in any lead but well formed chain discharges, whether fast or slow, usually prefer anterior over posterior areas of the brain.

Accompanying Clinical Symptoms

Dart-dome discharges lasting less than 3 sec. almost invariably are asymptomatic or "subclinical." A brief blunt spike-hump discharge is not accompanied by detectable unconsciousness, but there may be a fall or head nodding (astatic or inhibition seizure) or else a simple quick contraction of muscles (myoclonic jerk). The jerk is synchronous with the spike, which may be either sharp or blunt. However, a puzzling point, the spike-wave combination, and not a spike alone, seems necessary for the jerks and, also, a solitary spike-wave may or may not be accompanied by visible movement.

Figure 1 contains 6 separate spike-wave discharges from the record of a 26 mo. old boy, L. B., without significant history of etiology. For 10 mo. he had been having frequent daily falling and nodding (astatic) attacks and myoclonic jerks. Recently he experienced 5 convulsions. Petit mal phenomena had improved dramatically under tridione therapy. His EEG, made after 3 days without

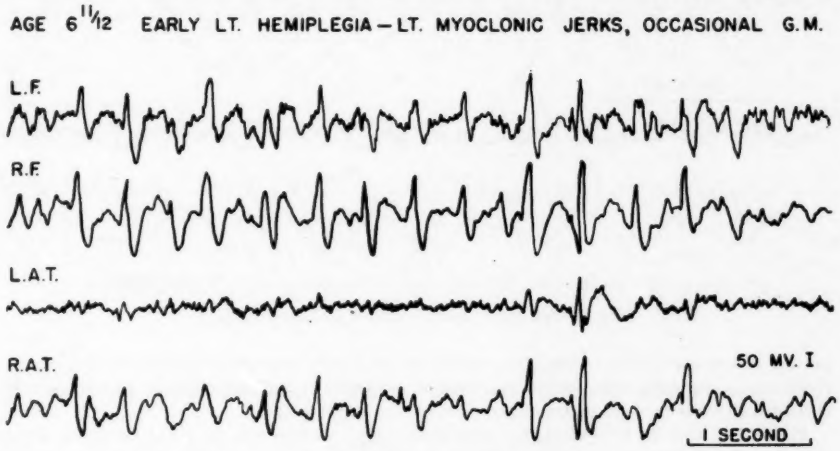

FIG. 3. EEG in Patient S. DeR.

medicine, contains spike and spike-wave discharges that recur from 5 to 20 times/min. Distribution of these discharges, their configuration and the relationship of spikes to waves differ in different leads. Visible bilateral muscular jerking accompanied all but the second and fifth of the series. Representation in all leads and multiple spiking of discharges seemed important for jerking but visible movement accompanied only a minority of such discharges.

Solitary blunt spike-hump discharge may accompany a falling or head nodding epilepsy also, but with the child recumbent during the recording, correlation of a seizure discharge with failure to maintain posture may not be easy.

Occasionally blunt spike-hump couplets may occur in chains. Dart-dome chains that accompany "petite absence" are of machine-like precision in spacing and in pattern (like a string of cut-out paper dolls). In contrast, slow couplets vary in spacing, in configuration and in distribution in various leads.

Figure 2 provides comparison of 3/sec. and 2/sec. spike-wave dysrhythmias and their accompanying symptoms. The left panel is of an intelligent 11 yr. old girl, K. McN., without significant history, who has had frequent daily "petite absences" for the past 3 yr. History and EEG of her monozygotic twin sister are nearly identical. There are 2.75 couplets/sec. During the "petite absence" the child was completely unconscious and motionless except for rhythmic blinking of eyelids, synchronous with spikes of the EEG. Right panel is a recording of M. McI., a girl 8½ yr. of age, with congenital brain damage. Since the age of 3 yr., she has had frequent daily head nodding and falling attacks, myoclonic jerks and frequent convulsions. Mental deterioration and bad behavior have been progressive. She has hours

or days of being in a mental fog, although conscious and able to respond to directions. The recording was made during such a period. Many spikes are sharp and stubby. Spacing of couplets is irregular. Arrows point to a focus of slow diphasic spike and hump in the R. anterior temporal and parietal leads. Some spikes are present on the R. and absent on the L.

When the continuity of couplets is interrupted or when they do not appear in all leads, recognizable discrete symptoms are less likely to attend. For example, Figure 3 is from the EEG of S. DeR., a girl nearly 7 yr. old. An aunt was epileptic and the child's birth was traumatic. At 13 mo. she began to have limp, vague periods and myoclonic jerks. Then she suffered a L. hemiplegia which has persisted and at present myoclonic jerks are L. sided. She also has periods of nystagmus and an occasional convulsion. EEG contained throughout almost continuous high voltage diphasic spikes in the frontal

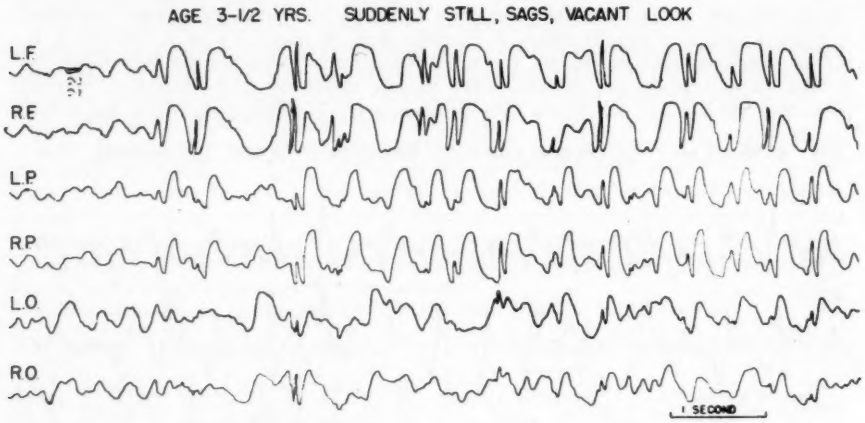

FIG. 4. Tracing at onset of seizure in Patient N. R.

and the R. anterior temporal leads. These spikes are irregularly placed with reference to slow waves, presenting an atypical picture. Patient was without symptoms during the recording, possibly because of limited distribution of discharges or preponderance of simple spikes.

Figure 4 is from the EEG of M. R., an adopted 3½ yr. old boy, who for a year has had a variety of seizures: an occasional convulsion or myoclonic jerk, and numerous daily falling (astatic) attacks, often with injury. What the mother calls "swims" recur many times a day and last for from 5 to 30 sec. He also has had long remissions of all symptoms with medication. EEG shows onset of one of his "swims." The patient abruptly "freezes," has a vacant look of apparent unconsciousness and sags a little without falling. Frontal leads of the EEG present a disorderly slow wave rhythm with spikes that are sharper than usual. These spikes recur at an average rate of 1½ per sec., but the interval between the 2nd and 3rd is 3 times the interval between the 5th and 6th. Waves are less obese in parietal than in frontal leads and have almost disappeared from the occipitals.

Figure 5 is from an infant 1 mo. of age, D. D. Her L. arm and leg had been twitching occasionally for 3 wk. but, after an operation for correction of a tracheo-esophageal fistula, movements recurred every few minutes. A focus of abnormality persisted in all leads from the R. cerebrum. Spikes seen in R. frontal and occipital leads were synchronous with the twitching. Waves from the 2 parietal leads are out of phase.

Figure 6 illustrates a spike-wave of extreme slowness, only 0.7 of a couplet from spike to spike per sec. The child. G. M., is an infant 10 mo. of age whose L.-sided convulsion with fever began 3 days before. There was twitching of L. arm and leg during the recording. Though slow waves were present in most leads, discrete spikes appeared only in R. parietal.

Figure 7 is of an 8 yr. old boy, E. K., who has incoordination and diminished size of the L. arm, probably the result of congenital cerebral defect or brain injury, although his PEG was normal. At 6½ yr. of age, he began to have generalized tonic convulsions which have recurred at irregular intervals. Astatic attacks began 2 mo. later and have increased to a frequency of several times daily.

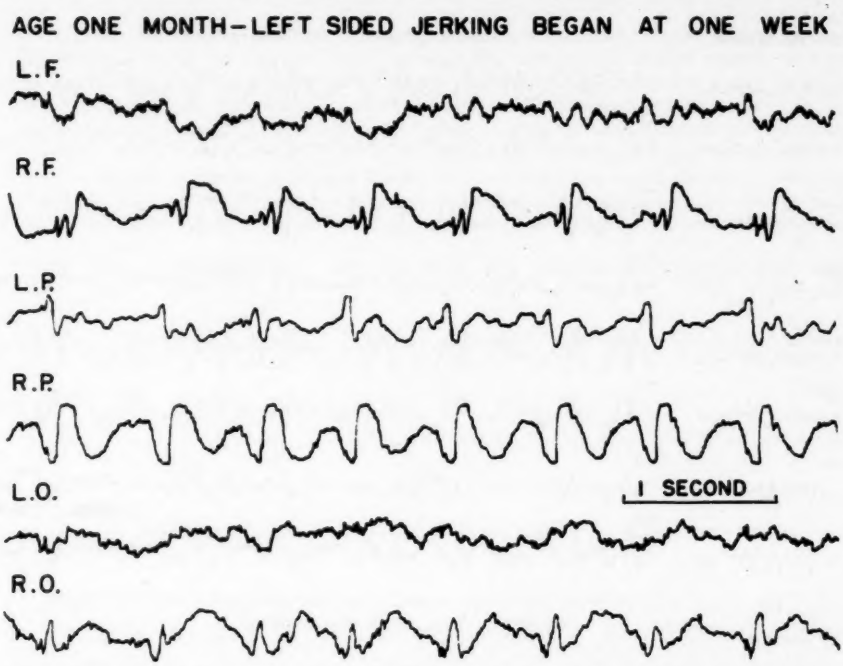

FIG. 5. Tracings from V. G. who was having periods of left-sided jerking during recording.

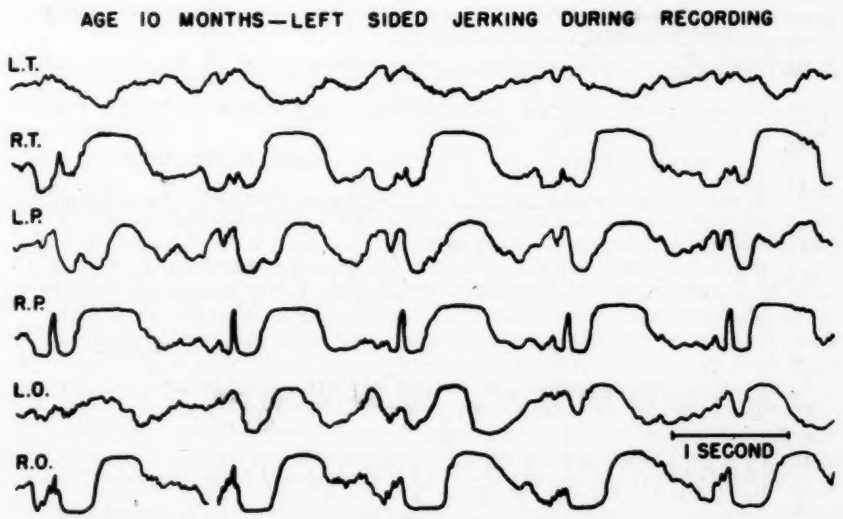

FIG. 6. Tracing from Patient G. M.

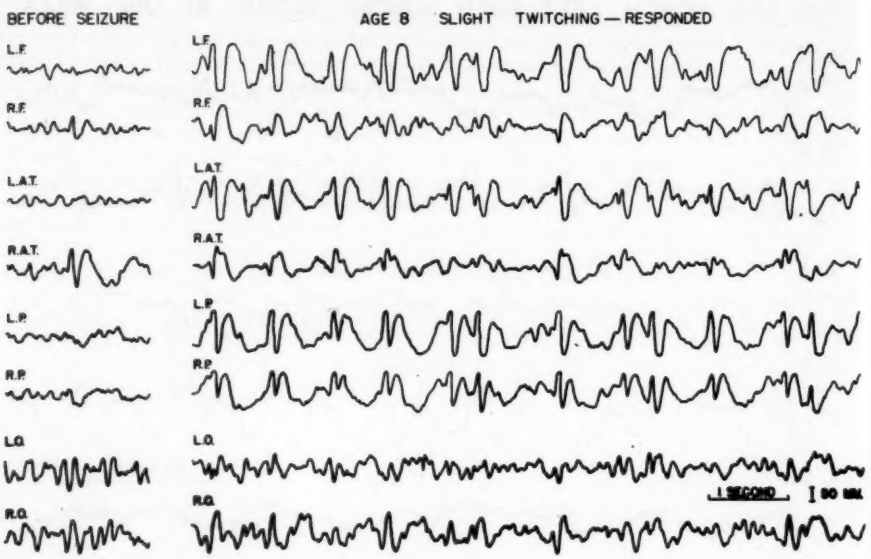

FIG. 7. EEG of E. K. before and during seizure of limpness and slight muscular twitching, apparently without loss of consciousness.

Unmanageable at school or home, he has set a number of fires. His I.Q. is 72. His EEG contains blunt spike-hump discharges that recur singly every 5 to 2 sec., with maximal representation in the R. parietal, temporal and anterior temporal leads. One such discharge appears in the left panel of the figure. During a 30 sec. period there were continuous high voltage slow spike-wave discharges, highest in the R. frontal, R. anterior temporal and L. occipital leads. During the recording, patient was limp with slight muscular twitching, but in spite of the widespread brain storm he responded when spoken to. Dysrhythmia subsided gradually.

Figure 8 is of a boy, A. C., aged 3½ yr., whose roentgenogram of the skull suggested arrested

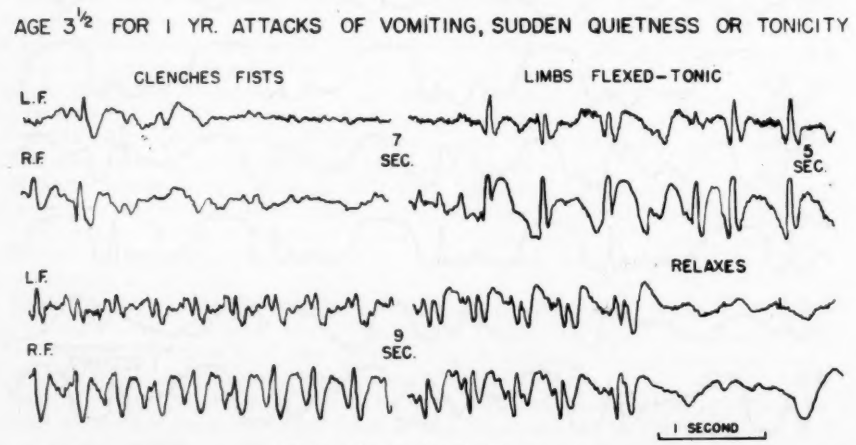

FIG. 8. EEG of A. C. before and during attack lasting ½ min. in which there was slight tonicity and loss of consciousness. Another section of record, together with recording after treatment 14 mos. later, is in Fig. 15.

brain growth. One year ago he began to have seizures of vomiting, then times of sudden quietness, generalized twitching and sleep. He would awaken in the night, scream, swallow rapidly, and when spoken to might say, "Get that dog away." He has had 3 convulsions. In present attacks, he stands still, clinches his fists, bows his head and swallows repeatedly. Such an attack accompanied the recording. Scattered spikes or spike and wave formations were present throughout the preliminary recording. For 10 sec. these were replaced by low voltage fast activity during which fists were clinched, perhaps in response to an aura. During 23 sec. of continuous seizure discharge, limbs were flexed and fixed and the patient apparently was unconscious. Dysrhythmia extended through all 8 leads, but the blunt spike and hump was largest and most nearly typical in R. frontal lead. Spacing

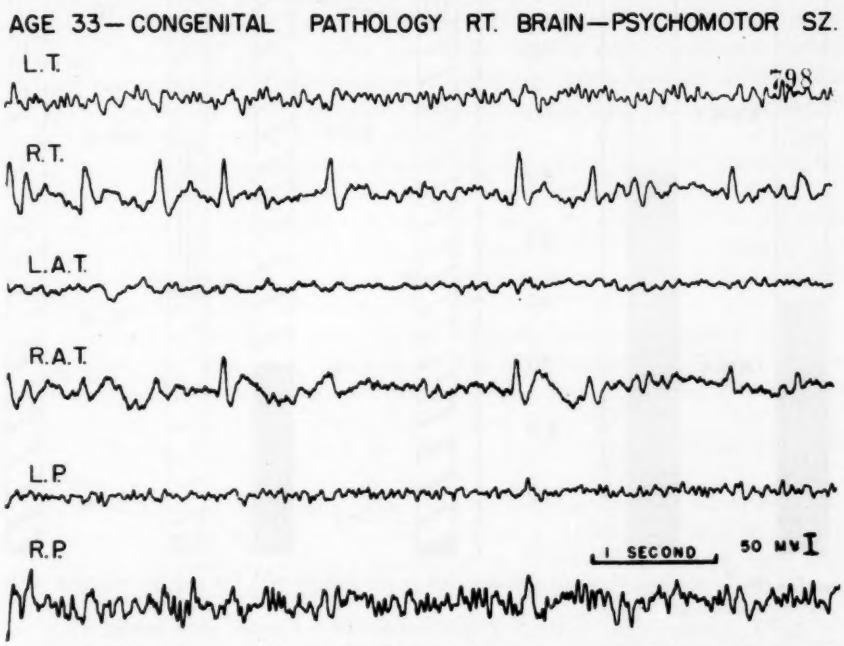

FIG. 9. EEG of woman 33 yr. of age with pathologic changes due to congenital hemangioma of R. cerebrum.

was irregular, and a blunt spike might appear on a wave as well as between waves. Frontal lead asymmetry, pronounced through most of the seizure, disappeared toward the end. Flattening of waves before the seizure resembles grand mal experience, although in appearance the seizure would be classed as psychomotor. Improvement of this EEG under medication is seen in Figure 15.

Figure 9 possibly represents the evolution of the blunt spike-hump formation with age. A woman, M. W., 33 yr. of age, had congenital hemangioma of the R. cerebrum, demonstrated by biopsy. Her L. arm is smaller than the R. There was a brief convulsion at the age of 2 yr. Attempted roentgen ray therapy resulted in permanent loss of hair from the scalp. Seven years ago, she began to have automatisms which now recur several times a day. In keeping with the history of psychomotor attacks, the EEG contains frequent negative spike discharges in the R. temporal lead and occasional blunt spike and hump discharges in the R. anterior temporal lead. There is also abnormally fast activity in the R. parietal and L. occipital leads. Presumably the discharges have been present from early life though chronic seizures have appeared only recently.

The frequency of slow spike-wave formations in the young and their rarity in adults raises the question whether these discharges or the persons who possess them die. Long term follow-up observations will be required for the answer. We know that the dart-dome dysrhythmia tends to die.

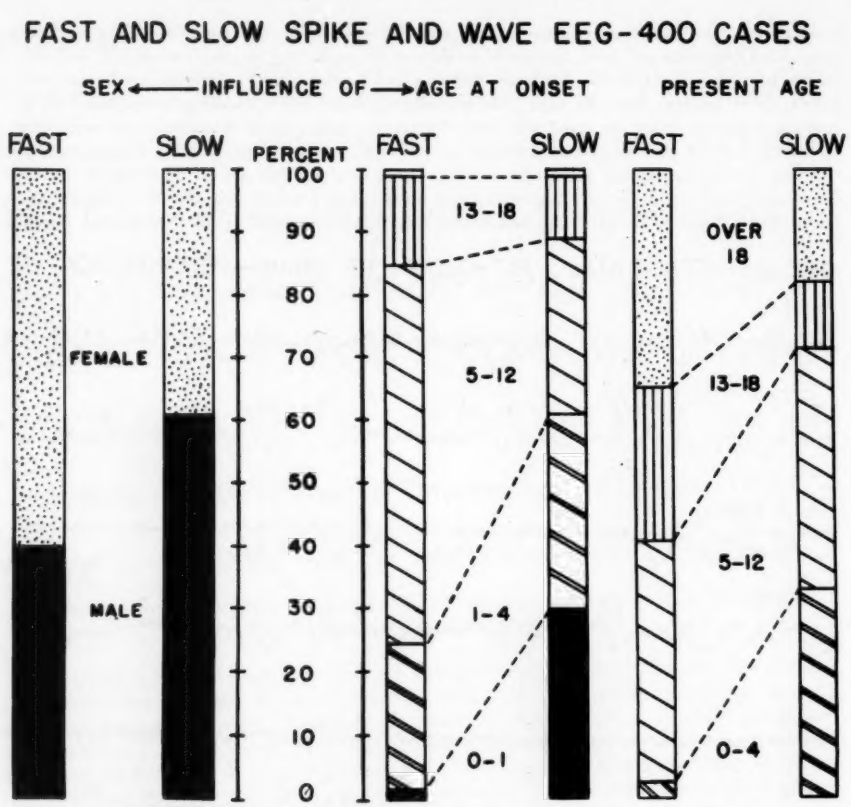

FIG. 10. Comparison of certain statistical data in 200 patients with fast and 200 with slow spike and wave discharges in EEG.

Two L. columns compare incidence of males and females in 2 groups. Males formed 40% of fast group and 61% of slow. Two central columns represent for 2 groups age of patient at time of first seizure. Percentage figures for fast and slow groups, respectively, are as follows: infancy, 2% and 30%; 1 to 4 yr., 22.5% and 30.5%; 5 to 12 yr., 60% and 28%; 13 to 17 yr., 14.5% and 10%; 19 yr. and over, 1% and 1.5%. Two columns on right show comparative age of patient at time of examination. For fast and slow groups, respectively, percentage distribution is as follows: 1st 5 yr. of life, 2.5% and 33.5%; 5 to 12 yr., 38% and 38%; 13 to 18 yr., 29% and 10.5%; 19 yr. and over, 30.5% and 18%.

The cases that have been presented furnish evidence regarding the symptomatic expression of blunt spike-hump discharges. A solitary but generalized discharge may be accompanied by a myoclonic jerk or by an astatic seizure. Each of these is instantaneous and without observable loss of consciousness.

A continuous chain of slow discharges, if fairly generalized, may similate an atypical "petite absence": limpness, arrest of activity, but with retention or only "fogging" of consciousness. With lateralization of electric mal activity, there may be one-sided jerking synchronous with the spike discharges. Rarely, there may be tonicity, in place of clonus or flaccidity, so that attacks resemble those which are generally classed as brief psychomotor seizures.

Our data permit certain statistical comparisons of these two groups of patients.

Sex: In unselected groups, epilepsy does not seem to have a preference for sex. Significance may attach, therefore, to the fact that males formed only 40% of the fast group, but 61% of the slow (left hand columns of Fig. 10). The blunt spike and hump is usually based on pathologic changes and males are more liable to congenital defects and to traumatic accidents than females.

Age: The two middle columns of Figure 10 compare the ages of patients at the time of their first seizure, without respect to the type or the cause of such attack, and in all but a few cases without respect to the patient's EEG at that time. The last two columns compare the ages of patients at the time of examination, which examination included electroencephalography. The values represented by the various divisions on the columns are listed in the text below the figure. Plainly the slow group is much the younger with respect to the age at onset and also the present age.

Thus, a first attack in infancy occurred in only 2% of the fast group against 15 times that number, 30%, in the slow group. The number of patients who at present are under 5 years of age is 13 times greater in the slow than in the fast group. This discrepancy with respect to age has been noted by Gibbs, Gibbs and Lennox[4] in a group of 1,260 patients of all ages. Eighty per cent of those with the slow pattern and 65% of those with the fast were less than 20 years of age.

This relative youth of the patients in the slow group might be explained in three ways: first, greater degree of tendency to seizures (heredity) manifested by their early appearance; second, very early pathologic changes; third, a specific affinity of slow discharges for the very young. In reference to the last point, it seems strange that dart-dome discharges hardly, if ever, appear in the EEGs of children during their first 3 or 4 years of life.

Other Electroencephalographic Abnormalities: Tracings were selected on the basis of whether they contained one of the two formations in question. In the fast group, the dart-dome discharge was the only abnormality in half the cases. In 35% there was in addition a slight increase or decrease (F, or S, in the Gibbs classification[4]) in the frequency of the background rhythm. There was pronounced increase (F_2) or decrease (S_2) in frequency in 8.5% and in 6.5% there were either focal abnormalities or spike discharges.

In the slow group, blunt spike-hump discharges occurred alone in 58%, dart-dome discharges also in 11%, very slow frequencies (S_2) in 16% and high voltage slow wave or spike discharges in 15%. Thus, gross abnormalities (in addition to the spike-wave complex) occurred in 15% of the fast group and in 31% of the slow. This doubled percentage probably reflects a greater degree of neuropathologic change in the slow group.

Types of Seizures: The manifestations that may accompany alternate spike and wave discharges have already been discussed, whether these are fast or slow.

Patients whose tracings contain spike and wave discharges may have had seizures other than the type described. Thus, a child who had convulsions in infancy may, at the age of 8 or 10 years, have only petite absence. The rare patient with dart-dome discharges, but without history of having experienced any of the petit mal triad, was not included in the fast group. In this fast group, 44.5% had a history of petite absence, myoclonic jerks or astatic seizures only. In 55.5%, in addition to such a history, there had been convulsive or psychomotor seizures.

In the slow group, nearly one half (47%) gave no history of any of the petit mal quartette of seizures commonly associated with the spike-wave pattern. Seventy-one per

cent had convulsions or psychomotor seizures (with or without petit mal). (In the group of 53 cases summarized by Derbyshire and Arthur,[5] 94% had "convulsive states.")

The distribution of seizure types in these 200 "slow" patients appears in the right hand column of Figure 11. The number and percentages represented are as shown in Table I.

Myoclonic or astatic seizures accounted for most of the 34.5% exhibiting one or more of the petit mal triad. Fifty-three per cent of the slow group had had one or more

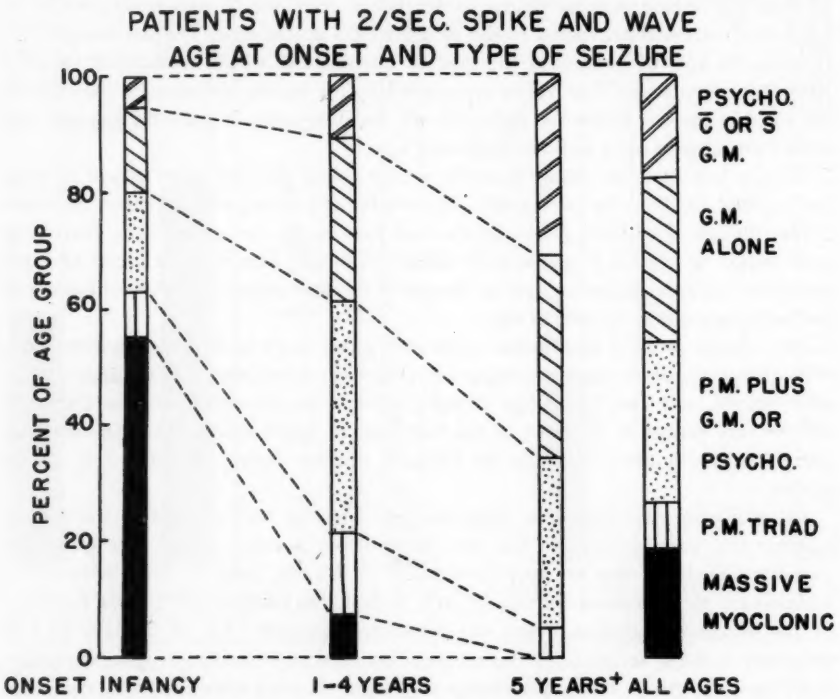

FIG. 11. Seizures or combination of seizures that have occurred in patients with slow spike and wave EEGs with respect to patient's age at time of first seizure, whatever its nature. Distribution of seizures for whole group is shown in R. column, and 3 different age groups in other columns, representing infancy, 2nd, 3rd and 4th yr., and 5th and later yr.

of what might be called the petit mal quartette, the fourth member being a type of seizure never observed in the patients having dart-dome dysrhythmia.

Massive Myoclonic Jerks: Eighteen and one-half per cent of this slow spike and wave group displayed seizures of a peculiar nature which we have called massive myoclonic jerks. Other forms of petit mal might be present also. This form of seizure, so common during the first few years of life, must have been observed frequently, but we have not encountered a specific description in English literature. The German "Blitz Krampf" probably refers to this type of seizure, though the term convulsion seems inappropriate for a single muscular contraction.

The infant (most often the child is under 12 or 18 months of age) suddenly flings

his arms upward or outward as in the Moro or startle reflex, and simultaneously flexes his head and draws his legs upward toward the abdomen. (A few infants have been observed to extend the legs, as in a tonic spasm). This jackknifing movement may be accompanied by a sharp cry, as of pain. The loss of consciousness, if any, is momentary. In its abruptness and brevity, the attack resembles a myoclonic jerk which is generalized, involving trunk muscles as well as those of the extremities. These massive jerks may recur in succession and form a series lasting from a few seconds to several minutes. The parents are distressed because they believe that the sharp cry is a response to pain. (One infant of this series was admitted to the hospital with a tentative diagnosis of intussusception.) However, the child does not continue to weep and, instead of being a reflex response to pain in a part of the body distant from the brain, the cry is probably the

TABLE I

Type of Seizures	Number	Per cent
Massive myoclonic jerks	37	18.5
One or more of petit mal triad	17	8.5
Triad plus convulsive or psychomotor	52	26.0
Convulsions only	56	28.0
Psychomotor possibly with convulsive	34	17.0
Unclassified	4	2.0
Total	200	100.0

expression of an electric discharge in the brain itself. Penfield has produced vocalization by stimulation of a certain point in the prerolandic area of the cortex.[6] We have seen one high school boy whose dart-dome myoclonic jerk was represented by a sharp vocalization.

Age at Onset and Type of Seizure in the Slow Group: Little study has been made of the time of life at which various seizure phenomena first appear, yet this is a subject of much neurophysiologic and practical importance. The slow group was separated into three parts: those whose epilepsy began in infancy, 30%; in the second, third and fourth years, 30.5%; in the fifth or later years, 39.5%. The distribution of types of seizures, enumerated for the whole group in the preceding section, is shown for these various age groups in the first three columns of Figure 11. When patients have a history of more than one type of seizure, the tabulation does not indicate which type appeared first. Therefore, most significance attaches to the histories of patients who have had but one type. Plainly, psychomotor and convulsive seizures, whether alone or combined, have their largest representation, 68%, in the oldest age group. The increase is at the expense of the massive myoclonic seizures. If epilepsy began in infancy, 55% of the babies had this form of seizure. Of all children having this type, 89% began in infancy and 100% in the first two years. The frequency of massive jerks in early life might be explained by the poorly organized state of the nervous system or by the relative frequency of pathologic processes. The relative infrequency of psychic automatisms might be related to neurologic development, or certain childhood aberrations of behavior might be precursor phenomena.

Type of Seizures and Electroencephalograms of Slow Group: As pointed out previously, the seizure history covers a period of years, and the electroencephalographic record a period of minutes—a fact that lessens the likelihood of significant correlations between the two. Even when patients have had but one type of seizure, the electroencephalographic

TABLE II

TYPE OF SEIZURE AND CLASSIFICATION OF EEG OF PATIENTS WITH SLOW SPIKE AND WAVE EEG

Type of Seizure	All Cases	Slow Spike-Wave Alone		Plus Fast Dart-Dome		Plus Slow Waves		Plus H.V.S.* or Spikes	
	No.	No.	%	No.	%	No.	%	No.	%
Massive myoclonic	37	21	56	0	0	11	30	5	14
Petit mal triad	17	5	29	7	41	3	18	2	12
Astatic, plus G. M. or psychic	52	26	50	10	19	6	12	10	19
Grand mal	56	37	66	5	9	6	11	8	14
Psychic with possibly G. M.	34	24	70	0	0	5	15	5	15
Unclassified	4	4	100	0	0	0	0	0	0
Total	200	117	58	22	11	31	16	30	15

* High voltage slow.

inter-seizure recordings are diverse, as shown in Table II. (This tabulation takes no account of records with mildly slow or fast dominant frequencies.) The proportion of records with the slow spike and wave alone, 58% for the whole group, varies from 29% in patients with only the petit mal triad, to 70% in those with psychomotor seizures—combined in some cases with convulsions. Three fourths of patients whose records contain dart-dome discharges have a history of one or more of the petit mal triad. In the combined group of 69 patients with a history of one or more of the petit mal triad (possibly plus convulsions or psychic seizures), 25% of the tracings contained the fast dart-dome discharge in addition to the slow form. These represent combined or hybrid cases of slow and fast formations. The fast form is conspicuously absent from the tracings of very young children with massive myoclonic jerks.

Evidence of Brain Damage: In epilepsy, two conditions importantly influence the

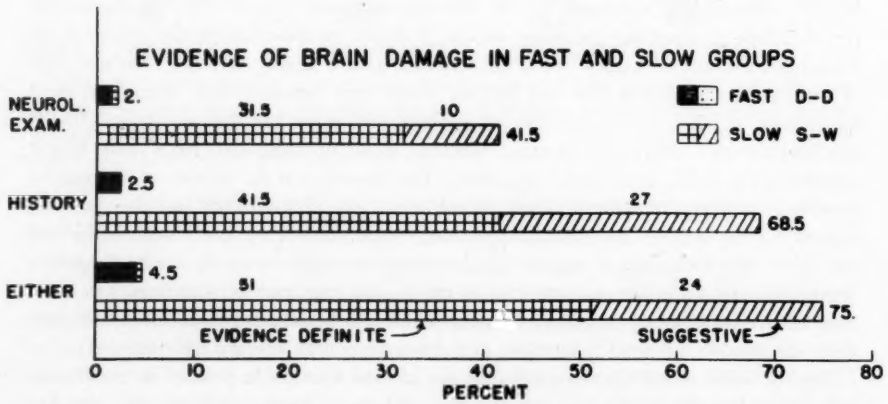

FIG. 12. For fast group, evidence, if definite, is indicated by solid column, if suggestive, by dotted portion. For slow group definite evidence is in squares, suggestive in diagonals. Figures denote percentages.

severity of the handicap and the prognosis. These are, first, the presence or absence of gross brain damage and, second, the patient's mentality. The rarity of a background of neuropathologic change in the 3/sec. dart-dome and its frequency in the 2/sec. variant has been noted but not studied. Any study is complicated by the presence of electroencephalographic abnormalities other than the spike and wave and clinical seizures other than the petit mal quartette.

In the fast group, more than one half (55%) had a history of convulsive or psychic seizures in addition to one or other of the petit mal triad. Nevertheless, only 4.5% had any evidence of neuropathologic change (Fig. 12). In four cases (2%), there were abnormal physical findings, definite in three cases and suggestive in one. (Findings were based on neurologic examination, the EEG and, rarely, the PEG.) In five other cases (2.5%), there was definite history of brain damage. In sharp contrast to this 4.5%, 75% of the slow group had evidence of brain pathologic change, this being definite in 51% and suggestive in 24%. The patient's history (definite or suggestive) provided

TABLE III

	Fast Group	Slow Group	
	No.	No.	Per cent
Birth injury or asphyxia	2	42	51.0
Encephalitis or meningitis	3	18	21.5
Prenatal (degeneration, injury, toxemia, etc.)	2	11	13.0
Trauma, concussion	1	5	6.0
Damage from initial convulsions	0	3	3.5
Tumor	0	2	2.5
Vascular anomalies	0	2	2.5
Total	8	83	100.0

more evidence than the physical findings (68.5% against 41.5%). However, evidence regarded as only suggestive was gained more often from the history (27%) than from the physical findings (10%).

Cause of Damage: The probable cause of the neuropathologic change, when this was definite, was determined for 8 of the fast group and for 83 of the slow. In the slow group, accidents at birth were believed responsible in one half of the cases; next in order of importance were infections of the brain, prenatal conditions, trauma, convulsions, tumor and vascular anomalies. The various causes in those cases in which the evidence was regarded as definite is shown in Table III.

Brain Damage and Type of Seizure in the Slow Group: Tabulation was made of the proportion of patients with various types of seizures that had definite evidence (by history or examination) of brain damage. This proportion was highest, 62%, in children with massive myoclonic jerks and lowest, 44%, in those with petite absence or simple myoclonic jerks (possibly with convulsions or psychic seizures). Intermediate were those with a history of convulsions only, 55%, or with astatic seizures (possibly with the addition of convulsions or psychic seizures), 54%. In patients with convulsions only, the history was especially important in establishing evidence of brain damage.

Genetic Influence in the Two Groups: This study demonstrates that neuropathologic change is more often present in the slow group. Therefore, the genetic factor might be

TABLE IV

Any Family History	Fast Group		Slow Group	
	No.	Per cent	No.	Per cent
Epilepsy alone	45	23.3	41	21.9
Migraine alone	31	16.1	19	10.2
Both	21	10.9	10	5.3
Neither	96	49.7	117	62.6
Total	193	100.0	187	100.0

considered of less importance. Comparison of the family history (when obtainable) of patients in the two groups yielded the results shown in Table IV.

This tabulation demonstrates the expected greater family history in the fast group. Sixty-three per cent of the fast and 37% of the slow group had some relative with epilepsy or migraine. Considering epilepsy alone, the respective percentages are 34 and 27%.

Although the genetic factor is relatively low in the slow group, it may not be absolutely low in comparison with a group of epileptics unselected with respect to their EEGs. The earlier seizures begin, the greater is the frequency of a positive family history of epilepsy. The epilepsy of 99% of the spike-wave patients began before the age of 20 years. For comparison, a study was made of the histories of 948 patients who were epileptic before that age, dividing these into an "acquired" group (those with evidence of brain damage antedating the first seizure) and a "genetic" group. Figure 13 compares the incidence of a family history of epilepsy in four groups of patients. A family history of epilepsy appeared in 26.1% of the 675 patients in the "genetic" group and in 20.8% of the 273 in the "acquired" group. The percentage spread between the two subgroups in the series of 380 and 948 cases is the same, 20%. The decreased incidence of heredity in the slow spike-wave group, as compared with the fast, can be explained by the increased evidence of pathologic change. However, the family history of epilepsy is as great in the slow spike and wave group (27.2%) as in patients with genetic epilepsy (26.1%). Therefore, we may conclude that the epilepsy of patients with the slow spike and wave pattern is built on both heredity and acquired neuropathologic change.

Mentality: The mental capacity of a patient is as important as seizures for his future.

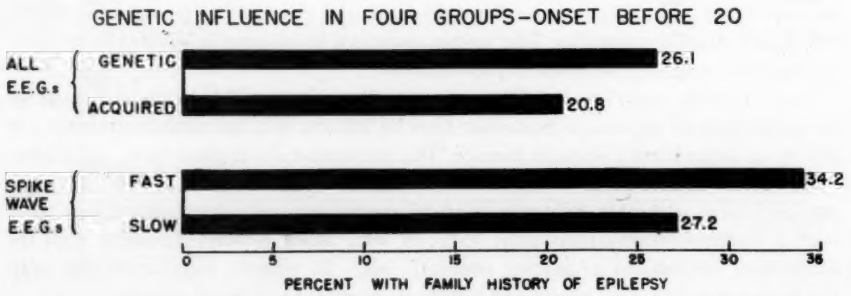

FIG. 13. Proportion of patients with family history of epilepsy. Uppermost bar refers to 675 "genetic" patients whose seizures commenced before age of 20 yr.; next bar, 273 with "acquired" epilepsy. Third bar 193 patients of fast group and last bar 187 of slow group. Respective percentages appear at ends of bars.

Three fourths of the fast group were given intelligence tests. In one fourth, and in the majority of the 190 in the slow group (because of their youth), the level of intelligence was judged by observation of the child and reports of his performance in such things as playing, dressing and feeding himself and the understanding or use of words. Four gradations were used: superior, an I.Q. of 120 or more; normal, 80-119; borderline, 70-79; subnormal, below 70. Table V, illustrated in the upper portion of Figure 14, gives the distribution of cases in the two groups:

Patients considered to be of borderline or subnormal intelligence formed 9% of the fast group and 61% of the slow. Conversely, persons of superior intelligence formed 20% of the fast group and only 5.3% of the slow.

TABLE V

	Fast Group		Slow Group	
	No.	Per cent	No.	Per cent
Superior	40	20.0	10	5.3
Normal	142	71.0	64	33.7
Borderline	7	3.5	27	14.2
Subnormal	11	5.5	89	46.8
Total	200	100.0	190	100.0

The studies of Collins and Lennox[7] have shown that petit mal (dart-dome "absence") is the kindest form of seizure on mentality.

Type of Seizure and Mentality in the Slow Group: As shown in the previous tabulation, 46.8% of the patients in the slow group were mentally subnormal with an estimated I.Q. below 70. Considering the data with respect to the type of seizure experienced (middle portion of fig. 14), subnormal mentality was observed most often in patients having massive myoclonic jerks, 74%, and in those with astatic seizures (plus convulsions or psychic seizures), 54%. These are seizure forms most intimately associated with the slow spike-wave. Only 38% of patients having convulsions only and 23% of those having psychic seizures (with or without convulsions) were retarded. These differences may mean that massive jerks and astatic (inhibitory) seizures involve pathologic change of portions of the brain intimately related to intelligence.

Brain Damage and Mentality in the Slow Group: Evidence from many sources, but especially evidence from monozygotic twin pairs affected by epilepsy,[8] demonstrates the importance of neuropathologic change in determining the intelligence of the epileptic. The present data, as shown in the bottom portion of Figure 14, are confirmatory.

Of 90 patients judged to be mentally subnormal, 68% had definite evidence in history or on neurologic examination of brain damage, in 21% the evidence was suggestive and was negative in only 11%. In contrast, among 74 patients of normal mentality, the percentage distribution in the three classes was nearly equal: definite damage, 36%; suggestive evidence, 34%; no evidence, 30%.

Response to Medication: As might be expected from the failure of the blunt spike and hump to respond to changes in blood chemistry,[2] as well as the frequency of underlying brain damage, drug therapy for affected patients is often unsatisfactory. When one or more of the spike-wave quartette of symptoms is present, tridione® or paradione®[9]

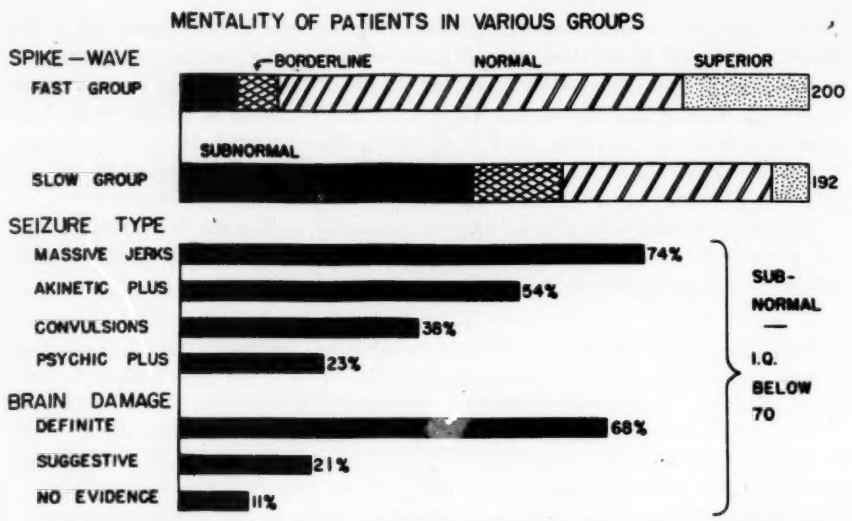

FIG. 14. Intelligence of patients in fast and slow groups and proportion believed to be mentally subnormal with reference to types of seizures and to evidence of brain damage. Upper 2 bars compare fast and slow groups. Data are in text. Remaining bars deal with patients of slow group who are mentally subnormal. Thus, of 37 children with history of massive myoclonic jerks, 74% were subnormal; of 104 patients with definite evidence of brain damage, 68% were subnormal, against 11% without such evidence.

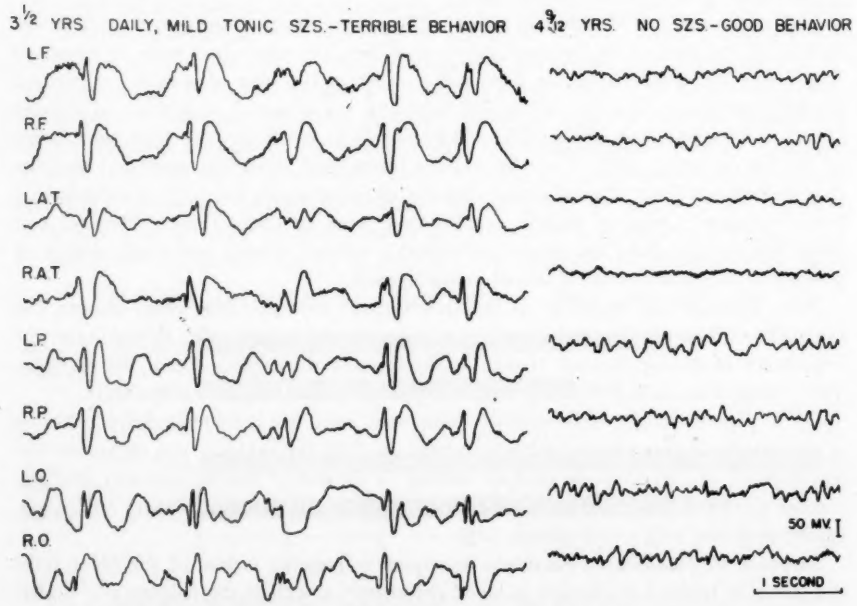

FIG. 15. Example of disappearance of blunt spike-hump discharges under treatment. In L. panel is another portion of EEG shown in Fig. 8. R. panel is from tracing made 14 mo. later when attacks were under control with phenurone®.

is the logical choice. When convulsive or psychomotor seizures are also present, then dilantin sodium®, mesantoin® or phenurone® may be used. In the present series of patients whose EEGs contained the 2/sec. formations, 140 were followed for variable periods of time. The seizures of 40 of these, or 14%, were controlled for from four months to five years. This 14% relief is less than half the number with dart-dome dysrythmia and "petite absence" who were seizure-free when taking tridione®. Of nine whose attacks were predominantly of the petit mal group, six were treated with tridione® or paradione®. Of 11 in whom other types of seizures predominated, seven took dilantin® and one each had tridione®, paradione®, mesantoin®, phenobarbital or amytal®.

Electric improvement usually lags behind clinical improvement. Nevertheless, in one group of 22 patients completely relieved of "petite absence," the EEGs of 16 (72%) lost their dart-dome formations.[10] The chance of eliminating the blunt spike and hump from a seriously affected EEG is much less, but this can happen. An instance of improvement is demonstrated in Figure 15. The left hand portion is from the same recording shown in Figure 8. This boy was having a number of mild tonic seizures daily and possessed an atrocious behavior. Under medication with phenurone®, the daily attacks of tonicity disappeared and had been absent for several months, together with absence of bad behavior. During a 20 minute recording (right hand panel of Fig. 15), not a single slow spike and wave appeared.

Summary

In order to test an hypothesis that slow spike and wave formations may be only the immature form of the 3/sec. dart and dome formation of "petite absence" and to learn more about the meaning of a dysrhythmia that consists of an alternation of wave frequency, a comparison was made of the clinical histories and examinations of 200 patients belonging to each group. The group with the slow pattern contained relatively more males; the patients were younger both when seizures began and at the time of examination, their history contained a greater variety of seizure phenomena and their EEGs more associated abnormalities. The evidence of brain damage that antedated seizures was much greater and the family history of epilepsy was somewhat less in the slow group as contrasted with the fast; and yet, heredity played as great a part in the slow group as in a large unselected group of "genetic" epileptics. Intelligence of the slow group was lower than that of the fast.

Slow spike-hump discharges are more diverse in configuration and distribution, more often localized and solitary than dart-dome discharges. The slow form is less often identified with specific clinical symptoms, though in this group of children, 53% had a history of one or more of the petit mal quartette. Astatic (akinetic) falls or simple or massive myoclonic jerks may accompany solitary discharges. Massive jerks were confined to the very young. Of the infants, 55% had this form. Periods of sudden stillness, staring, sagging, small jerkings or mild tonicity, often without full loss of consciousness, may be the clinical correlates of serial discharges. Though less responsive to tridione® or other therapy than the faster variety, control of seizures and even of this peculiar spike-hump dysrhythmia may be possible.

Conclusion

The property of alternation of wave frequency may bear a specific relationship to genetic (essential) epilepsy. The slow spike and wave formation does not represent

simply an immature form of the 3/sec. dart and dome pattern, but rather the confluence of three influences: extreme youth, heredity and neuropathologic change.

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SPANISH ABSTRACT

Correlación Clínica del Electroencefalograma de Onda-Espina Ligera y Lenta

Para probar una hipótesis de que formaciones de ondas y espigas lentas pueden ser solamente la forma inmatura de la formación de 3/sec. de flecha y cúpula de "petite absence" y para aprender más acerca del significado de una disritmia que consiste de una alternación de frecuencia de onda, hemos comparado las historias clínicas y los exámenes de 200 pacientes pertenecientes a cada grupo. El grupo con el patrón lento contenía relativamente más varones; los pacientes eran jovenes tanto cuando principiaron las ataques así como cuando se hicieron los exámenes, su historia de ellos contenía una mayor variedad de fenómenos de ataques y sus EEGs. más anormalidades asociadas. La evidencia del daño del cerebro que antedataba los ataques fué mucho mayor y la historia de epilepsia de la familia fué algo menos en el grupo lento en contraste con el ligero; y sin embargo, la herencia desarrolló un papel tan grande en el grupo lento como en un grupo no seleccionado de epilepticos "genéticos." La inteligencia del grupo lento fué más baja que la del ligero.

Las descargas de corcova de espiga lentas son más diversas en configuración y distribución, se localizan más amenudo que las descargas flecha-cúpula. La forma lenta se identifica más amenudo con síntomas clínicos específicos, aunque en este grupo de niños, 53% tenían una historia de uno o más del "petit mal quartette." Caídas "akinetic" o sacudidas mioclónicas simples o masivas peuden acompañar descargas solitarias. El último ataque nombrado fué limitado al más joven. De los infantes, 55% tenían esta forma. Períodos de calma repentina, fijación, combadura, pequeñas sacudidas o tonicidad suave, amenudo sin pérdida completa del conocimiento, pueden ser las correlaciones clínicas de descargas en series. Aunque menos responsivos a la tridiona® u otra terapia que la variedad más ligera, el control de los ataques y aún de esta disritmia espiga-corcova peculiar puede ser posible.

La propiedad de alternación de la frecuencia de onda puede tener una relación específica con la epilepsia genética (esencial). La formación de onda y espina lenta no representa simplemente una forma inmatura del patrón flecha y cúpula de 3/sec. sino que más bien la confluencia de tres influencias—es decir, extrema juventud, herencia y chambio neuropatológico.

300 Longwood Avenue

EFFECT OF GLUTAMIC ACID ON MENTAL FUNCTION

Pilot Study

By WILLIAM J. KERR, JR., M.D., AND S. A. SZUREK, M.D.
San Francisco

SINCE the observation of Price, Waelsch and Putnam[1] that glutamic acid, given to control epileptic seizures, caused "a degree of improvement in mental efficiency [that] could not be correlated with the incidence of seizures," much attention has been focused on the effect of the drug on mental function generally. Zimmerman, Burgemeister and Putnam[2,3] have been giving glutamic acid to groups of children with normal, subnormal and supernormal intelligence. They feel that there is definite improvement in the mental function of the retarded group; that there is evidence of improvement in the other two groups of a less degree. Further evidence that glutamic acid may have a specific effect on the brain is presented by Weil-Malherbe[4] who showed that glutamic acid was the only amino acid that could replace glucose as a substrate for brain slice respiration. Later work by Nachmansohn[5-7] showed that choline acetylase, an enzyme present in neural tissue, inactivated by dialysis was reactivated almost completely by glutamic and citric acids. Citric acid has not been tried clinically but is probably much too readily oxidized.

Because of the professional and lay interest in the potential value of this drug, the present study has been carefully conducted as a supervised experiment in an effort to evaluate therapy.* A small group (four) participated in the controlled group (Group A). One of these was removed from the hospital before the six months' period had elapsed. Another group of five children (one inpatient and four outpatients) were followed without control (Group B). The drug used was the laevo (plus) form of glutamic acid.† This is to be differentiated from glutamic acid hydrochloride, a racemic mixture of glutamic acid used principally as a source of hydrochloric acid. This latter drug was tried initially in experimental work on intelligence, but caused excessive gastric irritation in doses much above 5 gm. a day. A placebo‡ was prepared from glycine with sufficient tartaric acid to duplicate closely the taste of the glutamic acid. Tablets were of the same size, shape and color; were packaged in identical bottles—only the child's name appeared on the label. Only the three physicians in charge of the program and the pharmacist knew which child received which drug. This was done in an effort to eliminate any factor of attitudinal effect on the part of the psychologists or, even more important, the nursing staff. Dosage began at 5 gm./day and was increased by 1½ gm. every 7 to 10 days so that the final dosage was 33 gm./day for the inpatient group. This dosage was well tolerated by all the children. The outpatients received from 22.5 to 37 gm. as

From the Children's Division of Langley Porter Clinic and the Department of Pediatrics of the University of California Medical School, San Francisco, Calif.

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* Dr. Robert E. Harris, Mrs. Elaine W. Barron and Dr. Clare Wright Thompson, of the Langley Porter Clinic Psychology Department, aided in designing the experiment and supervising the intelligence testing.

† Purchased from Parke-Davis Company.

‡ The late Mr. Julian M. Wells, Chief Pharmacist of the University of California Hospital, assisted in the preparation of the placebo.

maximal dosage. One of the Group A children, receiving only placebos, vomited once at a relatively low dosage; later he took large doses without difficulty. A child in Group B developed gastritis on a relatively high dose but similarly took even greater amounts after a brief rest. No increase in muscular activity as described by Zimmerman was noted, although the average daily dose was as high as, and the final dose higher than, those reported by him.[2, 3]

The children in Group A all fell within the normal range as regards testable intelligence. Actually, inpatient children in a psychiatric hospital are ill in a way which makes it extremely difficult to be certain that they are participating adequately in a mental test situation. Of the children for whom it was possible to calculate an I.Q., there were four who could be divided into two pairs of the same sex and of approximately equal age and I.Q. One of each of these pairs (experimental) received glutamic acid; the other

TABLE I

	(1)	(2) IQ after 3 Mo.		(3) IQ after 6 Mo.	
	IQ before Treatment	#	Mean Change from (1)	#	Mean Change from (1)
Group A					
Glutamic Acid					
Male, 13 yr.	98	92	−10.5	115*	+2.0
Male, 5 yr.	112	97		99	
Placebo					
Male, 10 yr.	105	97	− 1.0	108	+3.0
Male, 7 yr.	92	98			
All Glutamic Acid—No Placebos					
Group B					
Inpatient					
Male, 6 yr.	Est. 50–70	Est. 50–70	None	Est. 50–70	None
Outpatients					
Male, 4 yr.	Est. 35–40	36	None	39	None
Male, 6 yr.	40	36		37	
Female, 13 yr.	61	68	+ 2.3	60	−2.3
Female, 10 yr.	55	59		52	

* This 17 point gain loses some of its weight, not only because the other child in the group lost 13 points, but because this same boy had gained 18 IQ points in the 5 mo. prior to glutamic acid therapy. On every occasion but the last, the examiner estimated the true intelligence to be higher than the test results.

(control) received placebos. Those in Group B were in the range from 35 to 70 and showed no evidence of marked emotional disturbance. These children were brought to the clinic by their parents in an effort to obtain glutamic acid therapy and not because of neurotic or hyperaggressive behavior. Unfortunately, an inpatient group of low intelligence was not available, but it was felt that the normal group would serve as a satisfactory pilot group since definite improvement had been reported[2, 3] in groups at all intelligence levels. Patients were tested on the Revised Stanford-Binet Intelligence Test, with the two forms administered alternately, before treatment and at three and six months

after beginning therapy. More frequent testing is felt to give excessive "practice effect." A different examiner, unfamiliar with the previous test results, saw the child at each test. The results are as shown in Table 1.

Conclusion

Administration of large doses of laevo (plus) glutamic acid to two children of normal intelligence produced no significant change in testable intelligence as compared with those receiving a placebo (glycine and tartaric acid). The average gain of those in Group A receiving glutamic acid was 2.0 I.Q. points; of those receiving the placebo, 3.0 points. This is close to the test-retest gain made by the group on which the scale was standardized by Terman and Merrill.[8] The members of the Terman-Merrill group, aged 5 to 16 years, gained 2.0 I.Q. points on the average from the administration of one form of the test to the administration of the alternate form two weeks later. Only estimates of pretreatment ability were available for two members of the low intelligence group. Tested after six months of therapy, they show no measurable change in intelligence with increasing age. The three other members of the low intelligence group after six months of therapy show a mean loss of 2.3 I.Q. points. (See Table I.) Children at this intelligence level frequently show some loss of measured intelligence with increasing age.[9]

Summary

These results do not substantiate previous reports that glutamic acid will increase measurable intelligence. Attitudinal effect on the part of nurses, psychologists and psychotherapists, which might influence the results, has been minimized by the use of careful controls and different psychologists in each test situation.

Because of the small number of cases here reported, further studies are needed on larger groups using similar controls. A hospital with a large stable population of children with low testable intelligence would be preferable to the Langley Porter Clinic. One such study is soon to be reported. The results are in essential agreement with these.[10]

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SPANISH ABSTRACT

Efecto del Acido Glutámico en la Función Mental: Estudio Piloto

La administración de grandes dosis de ácido laevoglutámico a niños de inteligencia normal no produjo ningún cambio de significancia en la inteligencia de prueba comparada con aquellos que recibieron un placebo (glicerina y ácido tartárico).

Nuestros resultados no soportan informes anteriores de que el ácido glutámico aumenta la inteligencia mensurable. El efecto de actitud de parte de enfermeras, psicólogos y psicoterapeutas, que pueden influenciar los resultados, han sido reducidos al mínimo por el uso de cuidadosos controles y diferentes psicólogos en cada situación de ensayo.

A causa del pequeño número de casos reportados aquí, se necesitan más estudios en grupos más grandes usando controles similares. Un hospital con una población grande y estable de niños con baja inteligencia ensayable sería preferible a la Clinica Langley Porter. Tal estudio será reportado pronto. Los resultados están de acuerdo con los nuestros.

University of California Medical School

INFANTILE TOXOPLASMOSIS

Report of a Case with Autopsy

By M. B. RODNEY, M.D., N. MITCHELL, M.D., B. REDNER, M.D., AND R. TURIN, M.D.
Brooklyn

SINCE the pioneer investigations of Wolf, Cowen and Paige[1-4] in the identification of a new type of protozoan disease in humans, particularly in infants, as toxoplasmosis, there has been an increasing number of cases reported in the literature. These authors described the characteristic symptom complex of convulsions, vomiting, fever and listlessness as indicative of central nervous system irritation. In those infants surviving the neonatal period, hydrocephalus and cerebral calcification could be demonstrated clinically. Ophthalmologic findings included microphthalmos, enophthalmos and chorioretinitis which was often bilateral. Other frequent clinical findings subsequently recorded included the presence of petechiae, jaundice, respiratory infections and cyanosis. The only abnormal laboratory findings suggestive of toxoplasmic infection were the spinal fluid findings of increased protein content, xanthochromia and pleocytosis.

The typical gross anatomic changes in the brain were focal leptomeningitis associated with subjacent cerebral cortical foci of necrosis. Scattered necrotic foci were also found throughout the brain with predominant localization in the basal ganglia. Hydrocephalus and focal cerebral calcification were frequent and striking accompanying changes. Spinal cord lesions typified by focal myelomalacia and brownish discoloration obliterating the normal landmarks of the cord were common findings. Microscopically, necrosis of neural and glial elements, acute and chronic inflammation, miliary granuloma formation, focal calcification and the presence of toxoplasmic parasites comprised the typical histologic findings.

The number of acceptable autopsy reports of infantile toxoplasmosis to date totals 20. Wolf and Cowen described their first case in 1937.[1] Wolf, Cowen and Paige subsequently reported a single case[2] and, later, three additional instances.[3] On the basis of typical findings, these authors rediagnosed four cases as toxoplasmic infection (Janku,[1] Torres,[5] deLange[3] and Richter[6]). A case recorded by Hertig[7] as sarcosporidiosis was later reviewed by Pinkerton and Weinman[8] and classified as toxoplasmosis. Steiner and Kaump[9] recorded a single case and alluded to the finding of parasites and characteristic histologic changes in a case referred to them by Sailer. In the same year, Zuelzer[10] reported two cases. Callahan, Russell and Smith[11] reviewed 10,000 autopsies and culled from this material five cases which they felt fulfilled the criteria for the diagnosis of toxoplasmosis. Since then, single case reports have been recorded by Pratt-Thomas and Cannon,[12] and Harwin and Angrist.[13] Buchanan and Lara-Gonzales[14] presented three autopsied cases, but the reports are fragmentary and neither gross nor microscopic descriptions nor photomicrographs accompany their presentation. For similar reasons, the case of Sailer, included in Steiner and Kaump's paper, and the cases of Adams et al.[15] are difficult to accept as proved cases of the disease.

From the Departments of Pathology and Pediatrics, The Beth-El Hospital, Brooklyn, N.Y.
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The disease is now being recognized more frequently, as the reports of Frenkel[16] and Stevenson[17] indicate. Schwarz[18] has tabulated 25 cases with autopsy descriptions which he listed as infantile but he has included three cases of Buchanan and Lara-Gonzales and one of Sailer which appear unacceptable because of the lack of clinical-pathologic and photomicrographic documentation. Tomlinson's case[19] was that of a 10 year old boy.

It is the purpose of this communication to describe the autopsy findings in a case of toxoplasmosis and to summarize briefly the anatomic findings in all the previously reported cases of infantile toxoplasmosis.

Case Report

Patient E., a male infant, was the product of an uneventful gestation and labor. He weighed 3.2 kg. and was 44 cm. inches long at birth. He appeared listless, pale and weak. The cry was weak and head turned spontaneously to the left. Skin was dry and shiny. Anterior fontanelle was level and not tense. A slight facial paresis was noted. Heart, lungs and abdomen were normal. Extremities were slightly edematous. A blood count revealed RBC 5.68 million/cmm. Hgb. 18.0 gm./100 cc., WBC 14.2 thousand/cmm. No erythroblasts were noted in the stained smear of the peripheral blood.

Condition was unchanged 2 days later except that he had lost 170 gm. Feedings were taken poorly and he was supported by clyses of 5% glucose in normal saline. A neurologic consultant noted a tendency to keep the right eye shut and the left eye open. Slight jaundice was noted also and the fontanelle was said to have a "doughy" feel. Upper extremities moved actively but lower extremities were sluggish after stimulation. At this time, examination of the blood revealed urea nitrogen 17 mg./100 cc.; total protein 6 gm./100 cc.; sugar 70 mg./100 cc. Examination of the spinal fluid revealed 11 WBC/cmm. with a 4+ Pandy reaction. Spinal fluid was xanthochromic.

Four days later, the infant was noted to have a flaccid paralysis of the lower extremities and retention of urine in the bladder with "voiding" of small amounts of urine at frequent intervals.

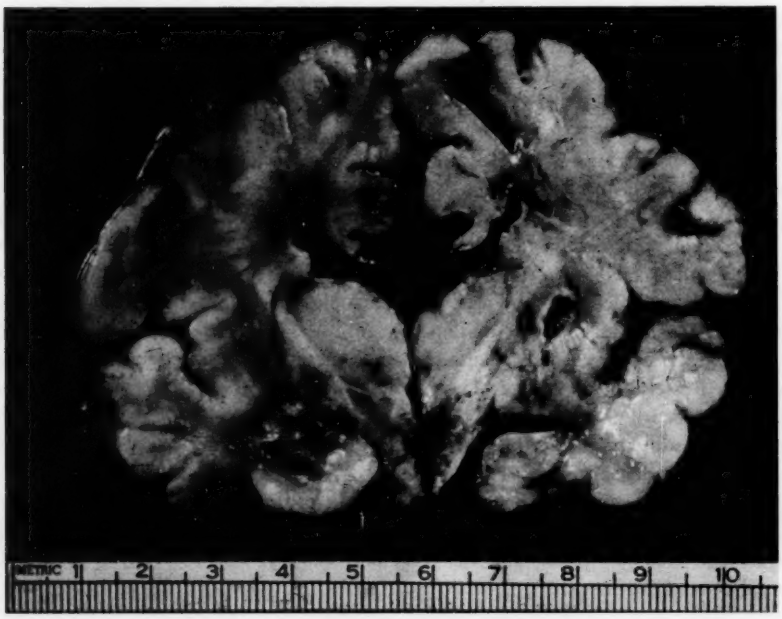

Fig. 1. Coronal sections through basal ganglia revealing large necrotic focus in L. lenticular nucleus and scattered foci in cortex of R. fronto-parietal region.

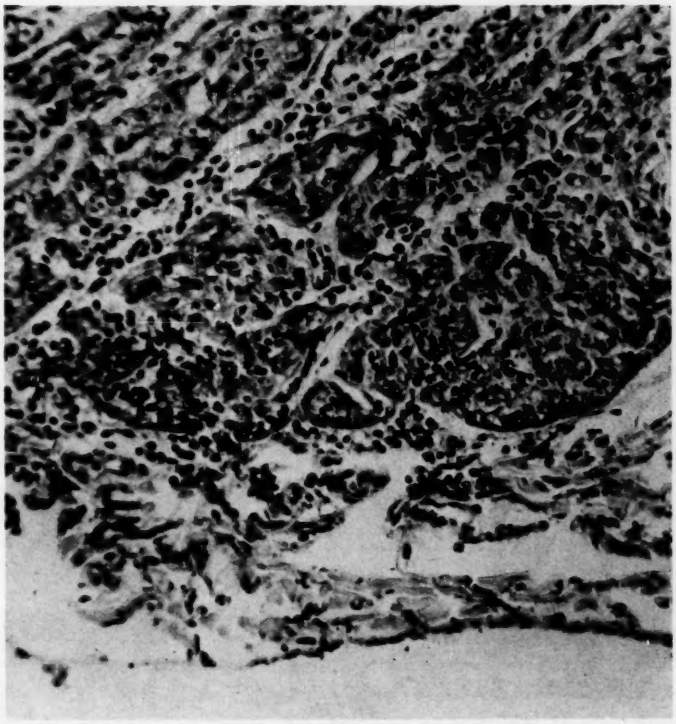

FIG. 2. Focal and diffuse myocarditis with round cell infiltration of myocardium and overlying epicardium. (230×) (All succeeding photomicrographs are from hematoxylin and eosin-stained sections.)

There were no spontaneous bowel movements and the abdomen was distended. On the 9th day of life, the patient showed cyanosis after gavage on 3 occasions. The next day a left sternocleidomastoid muscle paralysis was noted together with spontaneous horizontal nystagmus. Episodes of cyanosis increased in frequency and severity and continuous oxygen therapy was administered. Respirations slowed and became progressively more shallow. He died on the 12th day during an episode of cyanosis.

An interview with the infant's mother disclosed that there had been no illness in either parent during the entire period of gestation.

AUTOPSY FINDINGS

Gross Description: The body is that of a 12 day old infant weighing 2898 gm. Heel-to-crown length, 52 cm.; crown-to-rump length, 32 cm.; head circumference, 36 cm. Conjunctivae slightly congested. There is an excoriation of skin around the umbilicus. No subcutaneous lymph nodes are palpable. Serous cavities are lined by smooth and glistening mesothelial coverings with no excess fluid or adhesions. Heart weighs 27 gm. Myocardium is somewhat flabby with a pale brown red color. Lungs are slightly enlarged. Small bronchi contain slight mucopurulent exudate. Spleen is slightly enlarged, weighing 27 gm. It is soft and flabby with a dark reddish purple pulp and obliteration of the follicular markings. Liver lobules are well preserved. No foci of necrosis or hemorrhage are seen. Adrenal glands are pyramidal in shape. Architecture is well preserved. No foci of hemorrhage or necrosis. Bone marrow has a spongy pale red appearance. Brain weighs 405 gm. Covering membranes appear normal. The surface of the brain appears smooth and shiny. There are several round 0.5 to 1 cm. abnormal markings on the surface of the cerebrum. These markings

have a pale orange-yellow peripheral rim and a dark crescentic center. They have the appearance of an incomplete target. There are no abnormalities in the vascular system. The brain after fixation shows the yellowish plaques noted in the gross to be quite obvious in the leptomeninges. On section the foci just described are seen to be continuous with intracerebral foci of a similar nature. The intracerebral foci vary in size, ranging from 1.0 to 2.5 cm., the largest of them being present in the region of the basal ganglia (fig. 1). The foci of yellowish necrosis are scattered through all portions of the brain and in both cortex and subcortical white matter. There is no evidence of intraventricular involvement by the necrotic process; the choroid plexuses appear intact. Multiple sections through the spinal cord reveal obscure landmarks with a diffuse light pink discoloration present throughout. Both eyes are removed and after formalin fixation the choroid appears slightly thickened in many areas. Otherwise the usual ocular architecture is well preserved.

Microscopic Findings

Heart: Epicardium is moderately thickened and infiltrated by many large mononuclear leucocytes, occasional neutrophiles and lymphocytes and plasma cells. Myocardium shows both a focal and diffuse inflammatory infiltration (fig. 2) as well as focal necrosis of myocardial fibers. The inflammatory infiltration is predominantly mononuclear in type. Occasional neutrophiles and eosinophiles are found in the inflammatory foci. A rare parasitic cyst is found in some of the inflammatory foci. The individual parasites are ovoid blue bodies surrounded by a clear halo. The cyst contains between 10 and 30 individual parasitic forms.

Lung: Pulmonary architecture is somewhat distorted by the presence of an interstitial cellular infiltrate. The interalveolar septa are thickened and congested and contain large numbers of lymphocytes and large mononuclear leucocytes. Large phagocytic cells with eccentrically placed pyknotic nucleus and vacuolated cytoplasm are also found. Some of the alveolar lumens also contain a cellular inflam-

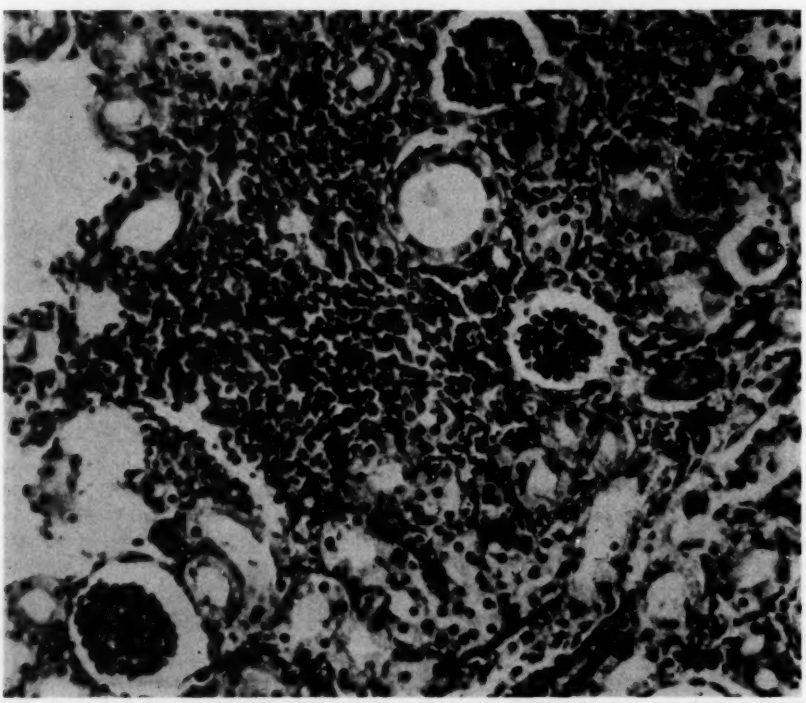

Fig. 3. Focal round cell interstitial nephritis. No parasites present in this focus. (250×)

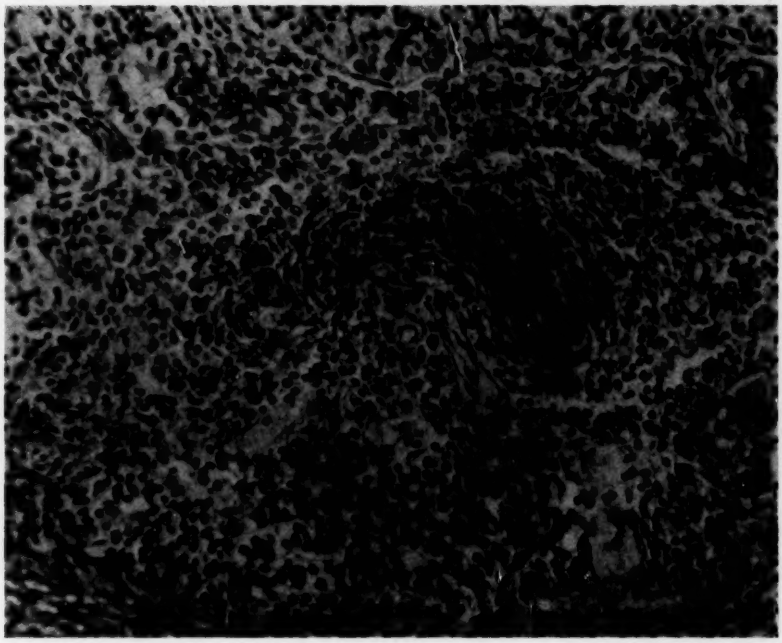

FIG. 4. Coagulative necrosis of seminiferous tubule is seen in center of photograph. Extensive interstitial orchitis is present throughout remainder of section with lymphocytes and plasma cells predominating. (230×)

matory exudate which is predominantly mononuclear in type. No parasitic forms are found in the lungs.

Spleen: Capsule and trabeculae are intact. White and red pulp are well differentiated. Moderate congestion of the red pulp and sinusoids is evident. A slight increase of immature myeloid forms is seen in the pulp. No parasites are found in the spleen.

Liver: Hepatic lobular architecture is well preserved. There is moderate congestion of the sinusoids. Many of the hepatic cells show limited fatty metamorphosis of the cytoplasm. In the portal triads there is a moderate number of inflammatory cells which are chiefly eosinophilic in character. No parasites are identified in the liver.

Kidneys: Capsule, glomeruli and tubules are essentially intact. In one section, in the superficial cortex immediately beneath the capsule, there is a large fairly well-circumscribed inflammatory lesion situated interstitially (fig. 3). The inflammatory infiltration is predominantly mononuclear in character although there are numerous eosinophiles scattered throughout. No parasites are identified in the renal parenchyma.

Bladder: Small circumscribed foci of chronic inflammation are present in the bladder mucosa. The bladder wall is moderately hypertrophied and diffuse as well as focal inflammatory changes are present throughout the muscularis and serosa. No parasites are seen in the vesical wall.

Testis: There is an extensive acute interstitial orchitis. The infantile tubules are in the main intact but an occasional one is the seat of an acute coagulative necrosis with a smudgy eosinophilic material replacing the seminiferous epithelium (fig. 4). The interstitial exudate is extensive and is seen throughout all the sections studied. Most of the cells are mononuclear in character. In many of the degenerating tubular cells parasitic forms composed of small bluish rods surrounded by a clear halo are seen. The parasitized epithelial cells are found especially in the vicinity of the focus of coagulative necrosis.

Brain: All the sections of the brain studied, including the cerebral hemispheres, brain stem and

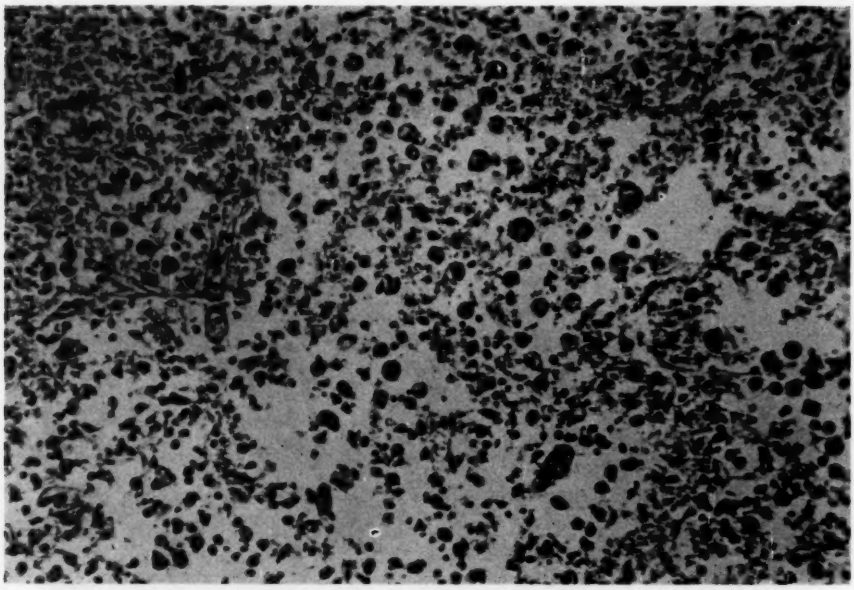

FIG. 5. Necrotic brain tissue with numerous gitter cells and acute and chronic inflammatory cells. (165×)

FIG. 6. Cystic focus of necrosis in basal ganglia region with eosinophilic material occupying center. Extensive inflammatory reaction present about necrotic focus. (65×)

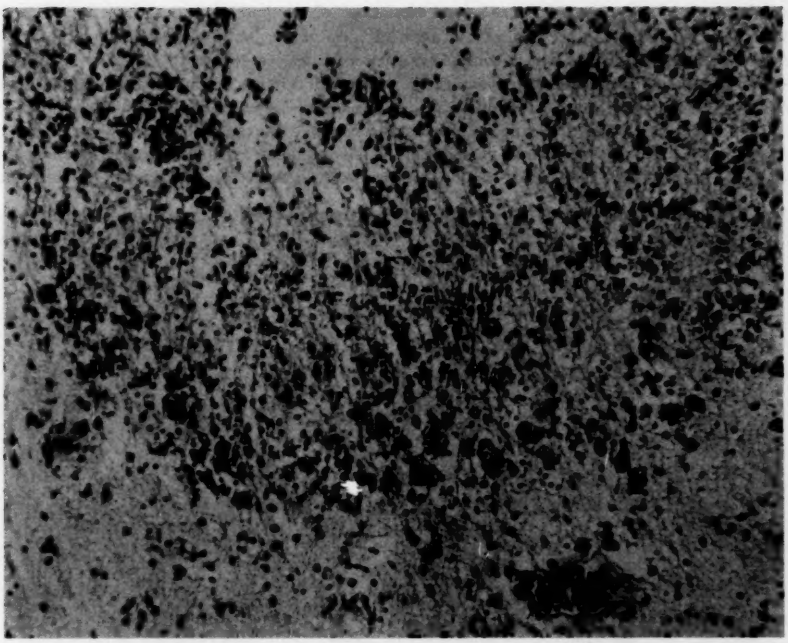

FIG. 7. Edge of cystic necrotic focus revealing calcification of necrotic nerve cells. (165×)

FIG. 8. Miliary granuloma formation in cerebral cortex. (165×)

cerebellum, show extensive diffuse and focal alterations of the parenchymal architecture. The most characteristic change is the presence of extensive necrosis of the brain parenchyma. In the necrotic foci extensive acute and chronic inflammatory reactive changes are present. Large lipophagic cells are present in plentiful numbers in many of the necrotic foci (fig. 5). In the foci of necrosis that are situated in the superficial cortex, overlying leptomeningitis is invariably present. Neural as well as glial elements are involved in the necrotic change. The blood vessels at the periphery of the foci of necrosis show a mantle of chronic inflammatory cells which are mainly lymphocytic and plasma cell in type. In several places the necrosis has progressed to actual cyst formation with the appear-

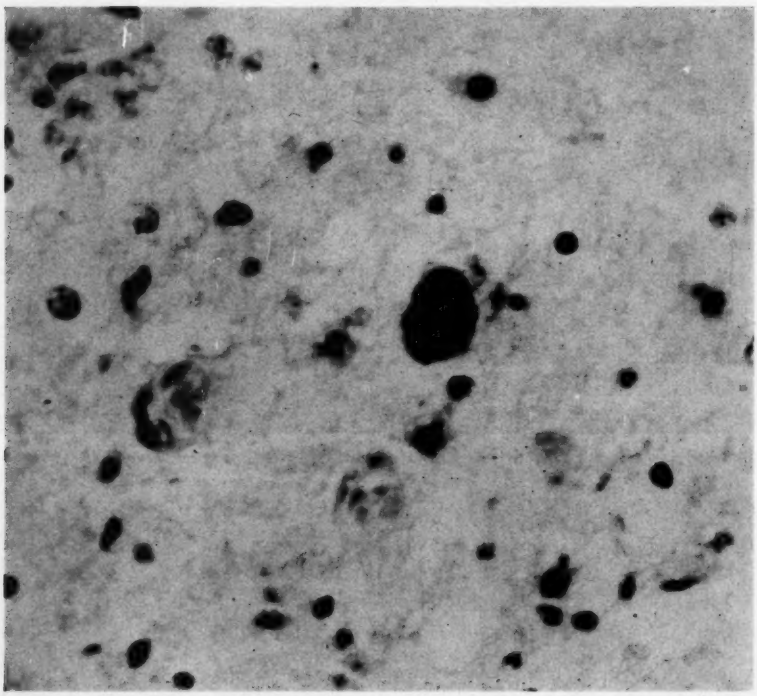

FIG. 9. Parasitic cyst in white matter of spinal cord. Individual blue-staining parasites are surrounded by clear halo. No reactive inflammatory changes are found in vicinity of parasite. (800×)

ance of a homogeneous eosinophilic material sometimes occupying the center of the cyst cavity (fig. 6). At the periphery of these cystic areas focal calcification of necrotic individual nerve cells is evident (fig. 7). Miliary granuloma formation both in the cortex and subcortical white matter is another change of prominence in the brain sections examined (fig. 8). These granulomas are composed of acute and chronic inflammatory cells and glial elements. Parasitic toxoplasmic cysts are found in many of the brain sections studied. The organisms are present not only in the necrotic foci but also in the vicinity of the miliary granulomas, in the perivascular regions and in cerebral tissue uninvolved by inflammatory change. Single parasitic forms in great numbers are identified in the necrotic foci.

In the spinal cord there is almost complete destruction of the normal landmarks. The grey and white matter are transformed into a mass of necrotic granulation tissue. A few isolated degenerating neurons can be seen in some sections of grey matter. Miliary granuloma formation is prominent and parasitic cysts are identified with ease mainly in the white matter and often unassociated with inflammatory reaction (fig. 9). In one section, acute inflammatory exudate is present within the central canal with ulceration of the ependymal lining.

Eye: All layers of the eye with the exception of the cornea are involved by an inflammatory and necrotic process. The predominant localization is in the choroid and retinal coats. In the retina there is focal destruction of the ganglionic and glial cells with replacement by an inflammatory exudate of mononuclear type. The basal layer of the retina is separated from the choroid by edema fluid. The choroid is greatly thickened in focal distribution by large dilated blood vessels surrounded by abundant subacute inflammatory exudate in which eosinophilic leucocytes and plasma cells are found in great number (fig. 10). The outer layers of the sclera show a chronic perivascular granulomatous inflammation of a similar character. Sections through the extraocular muscles show focal

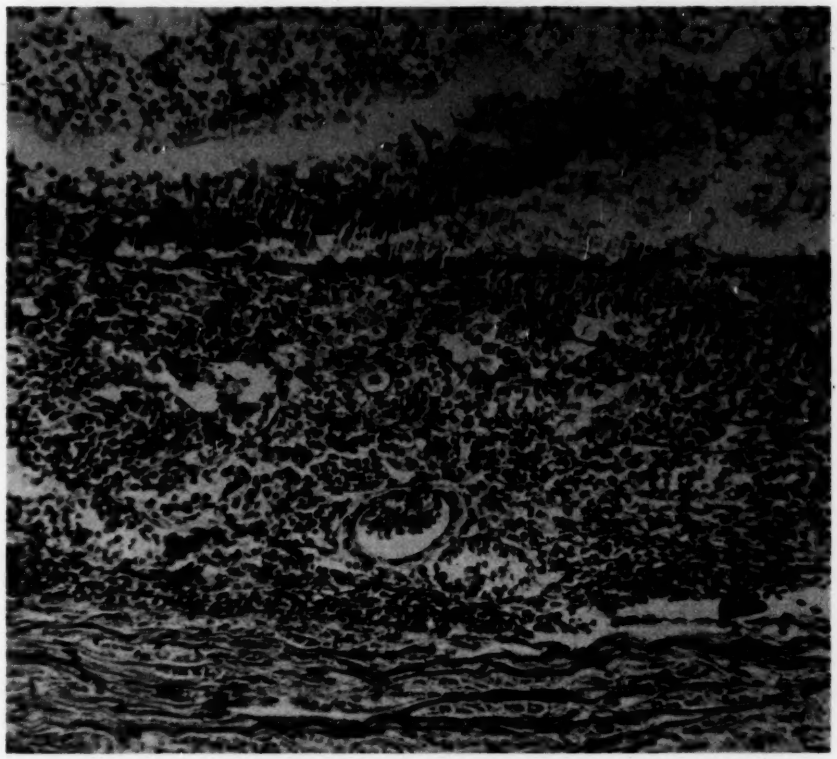

FIG. 10. Greatly thickened and chronically inflamed choroid coat of eye is separated from thickened and partially necrotic retina by layer of edema fluid. (165×)

destruction of the muscle fibers and subacute inflammation, interstitial in location. Parasitic cysts presenting characteristics similar to those seen in the brain and spinal cord are found in the extraocular muscles (figs. 11 and 12) and individual parasites are seen in the choroid and retina. The number of parasites in the cysts ranges up to 50 or more in number.

Skeletal Muscle: Sections of paravertebral striated muscle reveal a solitary parasitic cyst without surrounding necrosis of muscle fibers or inflammatory exudate.

DISCUSSION

Table I presents in outline form the 21 cases of infantile toxoplasmosis. Complete autopsy was obtained in 17 cases. There were 10 males and 11 females; two of the males were Negroes, the remaining 19 white. Eighteen of the 21 infants died before

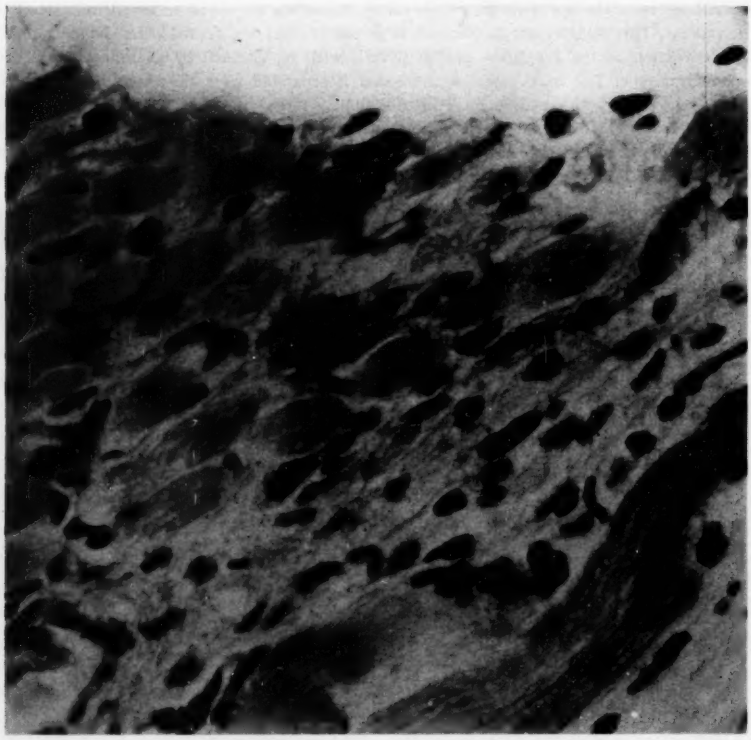

FIG. 11. Section through extra-ocular striated muscle reveals parasitic cyst in focus of partial destruction of muscle fibers with abundant reactive mononuclear exudation. (800×)

3 months of age. The maturity of 18 of the 21 infants was noted in the autopsy protocols. Of these 18 infants, 9 were full term, 8 were premature and one was postmature.

The three most constant and striking gross anatomic findings in the recorded cases were multiple foci of cerebral necrosis, calcification and hydrocephalus. The finding of necrosis in the cortex and white matter, with or without cyst formation, was practically universal. Calcification was present in 16 of 20 cases examined and hydrocephalus was found in 13 of 20 cases examined. In the spinal cord the lesions are less obvious, but often loss of architectural pattern and differentiation between the grey and white matter is obvious. No other characteristic macroscopic findings were noted in the viscera in the infantile cases.

Review of the microscopic findings in the cases reported in the literature substantiates the frequently noted observation that in infants the lesions are located predominantly within the central nervous system and the eyes, with less frequent though sometimes striking visceral lesions involving mainly the heart, striated muscle, genitalia, subcutaneous tissue and adrenal glands (Table II and III). In the case reported here, typical lesions with parasites were found in the cerebrum, cerebellum, brain stem, spinal cord, eyes, periorbital and paravertebral striated muscle, heart and testes. Inflammatory infiltrations containing no demonstrable parasites were seen in the kidneys and urinary bladder. Of

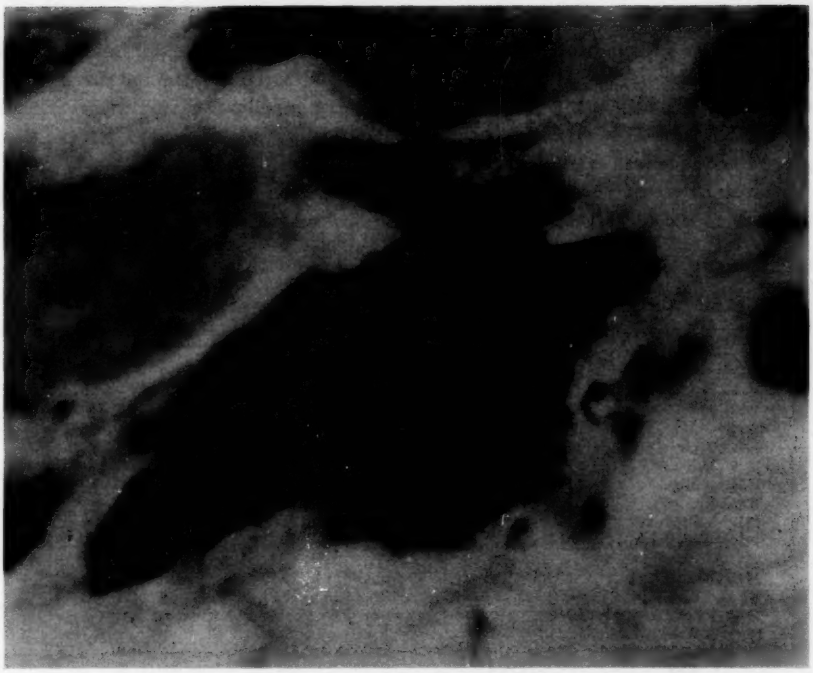

FIG. 12. Oil immersion photomicrograph of parasitic cyst seen in extra-ocular striated muscle. (3500×)

considerable interest is the involvement of the testicles. Except for a case of testicular involvement described by Zuelzer, the one described in this report is the only other instance of testicular involvement. However, the testicles were not examined routinely in most instances. They were examined in only 4 of the 11 males in the series. The importance of the testicular involvement lies in the possible transmission of the disease through venereal contact rather than through some of the other mechanisms suggested by previous authors.

TRANSMISSION OF DISEASE

Toxoplasmic infection of animals has been frequently reported and it is well known that the protozoan parasite infests a wide variety of different hosts, including the common household pets and pests. The epidemiology and pathogenesis of toxoplasmosis is at present obscure despite experimental investigations of this phase of the disease. In view of the known occurrence of toxoplasmosis in a great number of animals many authors have taken careful case histories in an attempt to elicit the presence of intimate contact and exposure to animals suffering from the disease. No proved cases of toxoplasmosis in an infant associated with a proved case of animal toxoplasmosis has come to the authors' attention. The role of an animal vector in the transmission of infantile toxoplasmosis thus remains vague.

The possibility that one mode of transmission of the disease may be venereal has received but scant attention. Wolf, Cowen and Paige suggested a local vaginal infection

with the parasites, with fetal transmission during parturition. The evidence pointing to an intrauterine inception of the disease in their cases as well as in other cases described forced these authors to discard this theory. Mesnil and Sarrailhé[20] showed that a diffuse toxoplasmic infection can be initiated in the guinea pig following intravaginal inoculation of the parasite. It is also believed that "dourine," a protozoan infection of horses caused by trypanasoma equiperdum, is transmitted by coitus.[21]

In contrast to the necrotizing granulomatous reaction occurring in infancy, toxoplasmosis in the older child and adult may follow an entirely different course. Sabin

TABLE I

AUTOPSIED CASES OF INFANTILE TOXOPLASMIC ENCEPHALOMYELITIS

No.	Yr.	Author	Sex	Age at Death	Period Gestation	Autopsy	Hydrocephalus	Calcification
1	1923	Janku	M	11–16 mo.(?)	?	Gross Brain Eyes	+	+(?)
2	1927	Torres	F	2 days	Full term	Complete	(not described)	
3	1929	DeLange	F	120 days	Term (3.0 kg.)	CNS	+	+
4	1934	Hertig	F	26 days	Premature (2 mo.)	Complete	–	+
5	1936	Richter	F	42 days	?	Complete	+	+
6	1937	Wolf, Cowen	F	30 days	Full term (4.4 kg.)	Complete	–	–
7	1939	Wolf, Cowen, Paige	M	31 days	Full term (3.0 kg.)	CNS	+	+
8	1942	Paige, Cowen, Wolf	F	63 days	Premature (3 wk.) (2.3 kg.)	Complete	+	+
9	1942	Paige, Cowen, Wolf	M (Negro)	Stillborn	Full term (2.6 kg.)	Complete	+	+
10	1942	Paige, Cowen, Wolf	F	3.5 days	Premature (6 wk.) (2.9 kg.)	Complete	–	–
11	1944	Steiner, Kaump	M	3 days	Premature(?) (2.1 kg.)	Complete	+	+
12	1944	Zuelzer	M	11 days	Postmature (14 days)	Complete	–	–
13	1944	Zuelzer	M	30 days	Premature (42 days) (1.5 kg.)	Complete	+	+
14	1946	Callahan I	F	31 days	Full term (2.8 kg.)	Complete	+	+
15	1946	Russell, Smith II	M	84 days	—	Complete	+	+
16	1946	Callahan III	F	65 days	Full term (3.4 kg.)	CNS	+	+
17	1946	Russell IV	M	64 days	Premature (2 wk.) (2.4 kg.)	Complete	+	+
18	1946	Smith V	F	3 hr.	Premature (3.1 kg.)	Complete	+	+
19	1946	Pratt-Thomas, Cannon	M	5 days	Premature (2.6 kg.)	Complete	–	–
20	1948	Harwin, Angrist	M	4 days	Premature (6½ mo.)	Complete	–	+(?)
21	1948	Rodney, Mitchell, et al.	M	12 days	Full term	Complete	–	+

has described an acute encephalitis in the older child. In the adult an entirely different clinical and pathologic picture is seen with a typhus-like clinical course and predominant localization of the parasites in the lung, liver and spleen (Pinkerton and Henderson[22]). Sylverton and Slavin[23] made the diagnosis of toxoplasmosis by finding typical parasites in the gastrocnemius muscle of an elderly white male who exhibited a clinical picture suggestive of trichinosis. Further, it may be stated that toxoplasmosis may occur as an entirely asymptomatic infection as indicated by the finding by Plaut[24] of toxoplasma-like organisms in the myocardium of a young boy who died of hepatitis. Since the clinical picture in the child may vary, it is entirely possible that latent asymptomatic involvement of the testicles may be a hitherto unrecognized possibility. The possible role of such asymptomatic testicular toxoplasmosis in the transmission of the disease must await further evaluation by study of more fatal cases.

TABLE II

VISCERAL INVOLVEMENT IN INFANTILE TOXOPLASMOSIS

Case	M 1	F 2	F 3	F 4	F 5	F 6	M 7	F 8	M 9	F 10	M 11	M 12	M 13	F 14	F 15	M 16	M 17	F 18	M 19	M 20	M 21
Organ																					
CNS	–	x	ox	T	ox	Tox	ox	Tox	Tox	Tox	Tox	Tox	Tox	Tox	Tox	Tox	ox	ox	Tox	ox	Tox
Eyes	To	–	–	–	–	Tox	ox	Tox	Tox	–	–	–	To	–	–	–	–	–	–	x	x
Heart	–	x	–	To	–	To	–	–	To	To	.	Tox	.	To	–	–	o	.	Tox	o	Tox
Lungs	–	–	–	T	.	.	–	–	.	To	.	T	.	.	.	.	.	.	T	–	.
Spleen	–	.	–	o	–	o?	–	–	.	o	.	.	.	–	.	–	.?	.	T	–	.
Liver	–	.	–	.	–	.	–	–	.	.	.	.	.	.	.	–	–	.	T	–	.
Pancreas	–	–	–	.	–	.	–	–	.	.	–	.	.	–	–	–	–	.	T	–	.
Adrenal	–	–	–	T	–	.	–	–	To	To	T	T	.	–	–	–	–	.	Tox	–	.
Kidney	–	.	–	.	–	.	–	–	.	.	–	ox	.	To	–	–	.	.	T	–	o
Testes	–						–		.		–	Tox	.			–	–		–	–	Tox
Ovary		–	–	–	–	.		–		Tox				–	–			–			
Uterus		–		–	–	.		–		–				–	–			–			
Bladder		–	–	–	–	–	.	–	–	–	–	–	–	–	–	.	.	–	–	–	o
Gastrointestinal	.	–	–	–	–	.	–	–	–	–	–	–	.	.	–	–	–	–	Tx	–	o
Thyroid	–	–	–	–	–	.	–	–	–	T	–	.	.	–	–	–	–	–	–	–	.
Thymus	–	.	–	–	–	.	–	–	–	–	–	–	–	–	–	–	–	–	T	–	.
Pituitary	–	–	–	–	–	.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	.
Striated muscle	–	x	–	–	–	.	–	–	To	T	–	Tox	.	–	–	–	–	–	–	–	Tox
Skin subcut. tissue	–	x	–	–	–	.	–	–	–	T	–	T	–	.	–	.	–	–	–	–	–
Bone marrow	–	–	–	–	–	.	–	–	–	.	.	.	–	–	ox	–	–	–	T	–	–
Umbilicus	–	–	–	.	–	.	–	–	.	T	–	.	–	–	–	–	–	–	–	–	–
Blood vessels	–	.	–	–	–	.	–	–	.	Tx	–	.	.	–	–	–	–	–	T	–	.
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	.	.	–	–	–	–	–	T	–	.
Diaphragm	–	–	–	.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	T	–	.

Key: T Parasites found—no inflamm. infiltrate.
. Examined—no lesion of toxopl.
o Typical inflamm. picture—no parasites.
x Typical inflamm. picture—parasites.
– Not described.

TABLE III

Organ	Cases Described	Cases Involved
CNS	20	20
Eyes	8	8
Heart	14	10
Striated muscle	7	5
Subcutaneous tissue	5	3
Testis	4	2
Ovary	2	1
Adrenal gland	10	5
Kidneys	12	4
Bone marrow	7	2
Lung	15	4

SUMMARY

A fatal case of infantile toxoplasmosis with autopsy findings is described, bringing to 21 the number of acceptable autopsied cases. The characteristic central nervous system necrosis and calcification were present in this case. In addition, focal chorioretinitis, involvement of the spinal cord and of the periorbital and paravertebral striated muscles and the heart were present. Of great interest is the finding of testicular involvement which has been described in only one other previous case.

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SPANISH ABSTRACT

Toxoplasmosis Infantil; Reporte de un Caso con Autopsia

Se describe un caso fatal de toxoplasmosis infantil con descubrimientos de autopsia, haciendo 21 el número de casos aceptables en los cuales se ha practicado una autopsia. La característica necrosis del sistema nervioso central, la calsificación e hidrocefalus estaban presentes en este caso. Además estaban presentes corioretinitis focal, complicación de la medula espinal ye de los músculos estriados periorbitario y paravertebral y el corazón. Es de gran interés el descubrimiento de complicación testicular, el cual ha sido descrito solamente en otro caso previo.

Rockaway Parkway and Avenue A

STUDIES OF PENICILLIN IN PEDIATRICS

III. Procaine Penicillin G in Sesame Oil, in Peanut Oil with 2% Aluminum Monostearate and in Water with Sodium Carboxymethylcellulose

By B. M. KAGAN, M.D., M. NIERENBERG, M.D., D. GOLDBERG, M.D., AND A. MILZER, PH.D., M.D.
Chicago

ONE of the objections to the earlier forms of penicillin preparations, particularly for use in pediatric practice, was the necessity for administration by intramuscular injection every three to six hours. Continuous efforts have been and are still under way to change the form of penicillin preparations so that a satisfactory concentration can be maintained over a sufficient length of time to kill the more resistant strains of infecting bacteria. The aim has been also to use the smallest number of injections, reduce the amount of pain and produce the minimum of untoward reactions.

In determining the dosage of penicillin to be given for a therapeutic response, a difficult yet important factor to be considered is the relation of the serum penicillin concentration to the concentration in the infected tissues. Although further study is needed to resolve this problem, one can proceed on the assumption that when infection occurs in an area where the blood supply is likely to be poor, the serum levels should be even higher than the concentration which inhibits the infecting bacteria in vitro. On the basis of much experimental work and of theoretic considerations, Eagle[1] considers that the serum penicillin concentration should be 2 to 10 times as high as the concentration desired in the tissues and that for areas which are relatively avascular, the level should be even higher.

The minimum serum penicillin concentrations, therefore, should be no less than the sensitivity in vitro of the specific infecting bacterium. It is now generally accepted that no single concentration can be considered as the minimum effective therapeutic concentration in all cases.[2] The minimum concentrations of penicillin in vitro which inhibit the growth of different species and even strains of infecting bacteria vary considerably. There is an optimum range of concentration of penicillin which is bactericidal for each strain.[1] Concentrations below this level are not bactericidal in vitro but may in some instances be effective clinically because of "host participation." One cannot, however, always depend upon the ability of the patient to "participate," especially when he is seriously ill.

The time required to kill organisms with optimum concentrations of penicillin varies considerably with different species and strains; e.g., between 1.5 and 35 hours. Studies

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From the Kunstadter Laboratories for Pediatric Research, the Department of Bacteriology and Virology, Medical Research Institute, and the Sarah Morris Hospital for Children of Michael Reese Hospital, Chicago, Ill.

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of a few strains have shown that the time required in the case of staphylococci is from 2 to 10 times as long as for Streptococcus hemolyticus and from 1 to 7 times as long as for pneumococci.[3] Because of these facts we have considered as the ideal that form of penicillin therapy which would, without producing untoward reactions, provide a continuous exposure of the infecting bacteria to an optimum lethal concentration over a sufficiently prolonged period of time.

Crystalline Na penicillin G in sesame oil gave no significant advantage over the same salt in water.[2] Crystalline Na or K penicillin G in peanut oil and beeswax, the first Romansky formula,[4] had a distinct advantage over all previous preparations. It permitted considerable prolongation of detectable blood levels. However, it was difficult to administer and was accompanied by undesirable local and sometimes general reactions.[5]

Results with a newer Romansky formula[6] in a similar menstruum, which is fluid at room temperature, was reported from this department recently.[2] When 4000 units/pound body weight of the potassium salt of crystalline penicillin G in the new type Romansky formula were given intramuscularly to infants and children between 4.5 and 18.0 kg. body weight, the following results were obtained: At 12 hours there was a minimum serum level of 0.32 u./ml. (average 0.60 u./ml. serum) and at 24 hours 94% of the subjects showed 0.04 u./ml. or more. Aside from occasional discomfort and some tender transient nodules, no untoward reactions to the new Romansky formula were noted in this series. However, in a few instances, sterile abscesses, painful nodules and allergic reactions were noted by other observers.

Procaine has been used for some time as an adjunct to reduce the pain caused by the intramuscular injection of penicillin. Recently it was found that procaine hydrochloride could be combined with crystalline Na penicillin G to form a salt of penicillin (procaine penicillin G).[7,8] Procaine penicillin has a low solubility in water and is therefore absorbed more slowly when injected intramuscularly. This results in prolongation of the penicillin concentration in the serum. Procaine penicillin is chemically stable at room temperature, thus requiring no refrigeration.

The first preparation available was procaine penicillin G in sesame oil. Subsequently procaine penicillin G in peanut oil with 2% aluminum monostearate and later procaine penicillin G in water with Na-carboxymethylcellulose and Tween 80 as dispersing agent became available.

The purpose of this study was to determine the blood levels which could be obtained in infants and children with various dosages of these three new procaine penicillin preparations and to compare these levels with those previously obtained with the new type Romansky formula.

Material and Method

All subjects were kept at complete bed rest. No parenteral fluids were given, but they were allowed to take fluid *ad lib.* by mouth. Subjects with evidence of renal, cardiac or hepatic impairment were excluded. Their weights varied between 4.5 and 18.0 kg. No newborn infants were included. The doses were measured and given by the same individual in each case and the blood specimens were withdrawn at carefully timed intervals.

The concentrations of penicillin in the serum were determined by a modification of the Kolmer serial dilution technic[9] using a standard Staph. aureus strain 209 P.* This

* Supplied by the Federal Security Agency, Food and Drug Administration, Washington, D.C.

organism is sensitive to penicillin 0.04 u./ml. Frequent checks showed that its sensitivity did not change throughout the course of the study.

Procaine Penicillin G in Sesame Oil

Sullivan et al.[7] reported that in 21 hospitalized adults given procaine penicillin in sesame oil 300,000 u. each, 20 had serum levels of 0.62 u./ml. or higher at the end of 24 hours. Herrell et al.[10] found that levels of at least 0.03 u./ml. were maintained for 24 hours in 9 out of 10 adult patients who were given 300,000 u. Robinson et al.[11] found that this dosage in adults gave a median level of 0.375 u./ml. at 12 hours and 0.125 u./ml. at 24 hours. They found detectable levels at 24 hours in 96% of their patients. In view of their data it seemed worth while to test this preparation in infants and children.

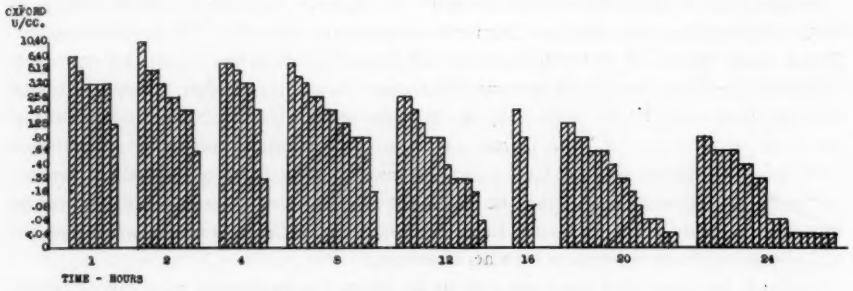

Chart 1. Penicillin Serum Levels Following Administration of Procaine Penicillin in Sesame Oil: 4000 u./lb. intramuscularly.
Ordinate is in Oxford u./ml. of penicillin. Each column of abscissa represents determination done at time intervals indicated on chart.

Crystalline procaine penicillin G was suspended in refined sesame oil*[12] in a concentration of 300,000 u./ml. A uniform suspension was obtained by vigorous shaking for at least two minutes. The suspension was withdrawn through a dry sterile needle into a dry sterile syringe, and the needle was replaced for injection. Needles of 20 gauge size were used.

Chart 1 and Table I show the results obtained in 20 subjects who were given 4000 u./lb. of procaine penicillin G in sesame oil. After an interval of 12 hours, the range of serum penicillin concentrations was 0.04 to 2.56 u./ml. (average 0.92 u./ml.). In comparison, the concentrations 12 hours after injection of 4000 u./lb. of penicillin in beeswax and peanut oil ranged from 0.32 to 1.60 u./ml. (average 0.60 u./ml.).[2] At 24 hours after injection, the range of serum penicillin concentrations with 4000 u./lb. of procaine penicillin in sesame oil was less than 0.04 u./ml. to 0.80 u./ml. (average 0.29 u./ml. considering seven of the determinations to be zero). With the same dosage of penicillin in beeswax and peanut oil the range at 24 hours was zero to 0.80 u./ml. (average 0.18 u./ml.).

Thus, in the same dosage per unit body weight procaine penicillin in sesame oil gave higher average serum penicillin levels at 12 and at 24 hours than did penicillin in beeswax and peanut oil. However, at 24 hours 35% of the subjects had no detectable levels with procaine penicillin in sesame oil and only 6% of the subjects given penicillin in beeswax and peanut oil had no detectable levels.

* Duracillin®, in oil, supplied by Dr. N. P. Sullivan, Eli Lilly & Company, Indianapolis.

TABLE I

SERUM PENICILLIN CONCENTRATIONS 12 AND 24 HR. AFTER INTRAMUSCULAR INJECTION OF PENICILLIN*

Preparation	Dosage u./lb.	No. Subjects	u./ml. at 12 hr.		u./ml. at 24 hr.		% of subjects with 0.04 u./ml. or > at 24 hr.
			Range	(average)	Range	(average)	
K penicillin G in peanut oil and beeswax†	4000	31	0.32–1.60	(0.60)	<0.04–0.80	(0.18)	94
Procaine penicillin G in sesame oil	4000	20	0.04–2.56	(0.92)	<0.04–0.80	(0.29)	65
Procaine penicillin G in sesame oil	8000	20	0.08–5.12	(1.90)	0.04–3.20	(0.83)	100
Procaine penicillin G in peanut oil with 2% aluminum monostearate	8000	27	0.40–3.20	(1.20)	0.04–1.60	(0.60)	100
Procaine penicillin G in water with Na-carboxymethylcellulose	8000	35	0.32–>6.40	(2.75)	<0.04–5.12	(1.06)	94

* Infants and children between 4.5 and 18.1 kg. (10 and 40 lbs.) weight, excluding newborn infants.
† Fluid at room temperature.

Hewitt et al.[13] found that when 600,000 u. of crystalline procaine penicillin G in sesame oil were given intramuscularly to adults the serum penicillin concentrations at 12 hours (average 0.37 u./ml.) were not particularly higher than when 300,000 u. were given (average 0.21 u./ml.). However, the most characteristic difference between the results obtained with these two dosages was found to be a "prolongation of a given penicillin level rather than an increase in magnitude of the penicillin concentration during the early period of its administration." At 24 hours, 300,000 u. gave an average serum

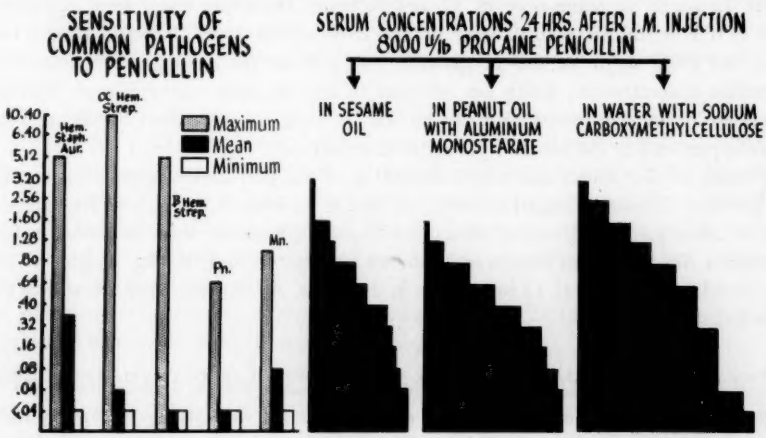

CHART 2

Ordinate is in Oxford u./ml. of penicillin. Abscissa under black blocked area represents numbers of cases: for sesame oil, 20 cases; for peanut oil with aluminum monostearate, 27 cases; for water with Na-carboxymethylcellulose, 35 cases.

concentration of 0.08 u./ml. whereas 600,000 u. gave an average concentration of penicillin in the serum of 0.18 u./ml. These averages were calculated from their charts.

Because of this, and because so many of our subjects given procaine penicillin G in sesame oil 4000 u./lb. had no detectable serum penicillin after 24 hours, the dosage was increased to 8000 u./lb. When the latter dosage was given to 20 subjects, the serum penicillin concentration at 24 hours was found to be 0.04 to 3.20 u./ml. (average 0.80 u./ml.; see Table I and Chart 2). All of these patients had serum penicillin concentrations of 0.04 u./ml. or higher at the end of 24 hours.

In view of the superior serum levels with this dosage, six patients were given 8000 u./lb. of this preparation every 24 hours for five days and the blood specimens were drawn just prior to the subsequent injection. The concentrations of penicillin in these cases were found to be between 0.04 and 3.20 u./ml. The average concentration was 0.97 u./ml. It would appear, therefore, that in spite of the high 24 hour concentrations, repeated doses of 8000 u./lb. at this interval do not result in significant increases in serum penicillin concentrations at the end of each 24 hour period.

Procaine Penicillin G in Peanut Oil with 2% Aluminum Monostearate

It was found that when procaine penicillin was suspended in a colloidal gel composed of peanut oil and 2% aluminum monostearate,*[14] the absorption of the penicillin was delayed even more. The size of the particles in this preparation was made small so as to permit more of the crystals to be coated with the gel and thus to be made more water repellent.[15]

Using this preparation, the same dosage per unit weight (8000 u./lb.) was given to 27 other infants and children. The concentration of penicillin in the serum after one hour was 0.04 to 10.24 u./ml. (average 5.0 u./ml.); after 12 hours it was 0.40 to 3.20 u./ml. (average 1.20 u./ml.); after 24 hours it was 0.04 to 1.60 u./ml. (average 0.60 u./ml.). None of these patients had concentrations below 0.04 u./ml. at the end of 24 hours. In six of the subjects at 48, 72 and 96 hours, the serum levels were, respectively, 0.04 to 0.64 u./ml., 0.04 to 0.08 u./ml. and 0.04 to 0.08 u./ml. It would appear, therefore, that 8000 u./lb. of this preparation may provide for as long as 96 hours serum penicillin concentrations which are adequate to kill the most susceptible of pathogenic organisms. This preparation provides 12 and 24 hour concentrations which are similar to those provided by the procaine penicillin in sesame oil.

Thomas et al.[15] found that when 300,000 u. of the preparation were given to adults, the levels at 12 hours averaged 0.104 u./ml. and at 24 hours 0.114 u./ml. This suggested a slow, albeit prolonged, rate of absorption. Our data, however, show that when a dosage of 8000 u./lb. is given to infants and children between 4.5 and 18.0 kg. weight the levels are considerably higher at 12 hours than at 24 hours. At one hour they are several times higher than at 12 hours.

Procaine Penicillin G in Water with Sodium Carboxymethylcellulose

In order to retain the advantages of the colloidal gel in delaying absorption and yet to eliminate the necessity for oil, procaine penicillin was suspended in a gel with Na-

* Flo-Cillin®, supplied by Dr. Wm. E. Crutchfield, Jr., of Bristol Laboratories, Syracuse, N.Y.

carboxymethylcellulose.*[11] Tween 80 was added as a dispersing agent. This preparation has an additional advantage in that it does not require the use of a dry syringe.

The same dosage per unit weight (8000 u./lb.) of this preparation was given to 35 other infants and children. The serum concentrations at 12 hours varied from 0.32 to greater than 6.4 u./ml. (average 2.75 u./ml.). The concentration of penicillin in the serum after 24 hours was found to vary from less than 0.04 u./ml. to 3.20 u./ml. (average 1.06 u./ml.; Chart 2). Of the 35 patients, 94% had serum penicillin concentrations of 0.04 u./ml. or higher at the end of 24 hours.

Warning About Accidental Intravenous Injections

Stollerman et al.[16] gave up to 1.0 cc. of procaine penicillin in water with Na-carboxymethylcellulose intravenously to dogs without untoward reaction. They therefore considered the possibility of accidental embolization with such aqueous suspensions to be minimal.

The following experience led us to investigate this further.

F. B.† was a 4 mo. old white female, weighing 5.5 kg. She was admitted for an upper respiratory infection following which she developed a protracted diarrhea. Immediately following an "intramuscular" injection of procaine penicillin G in water with Na-carboxymethylcellulose 0.5 ml., she suddenly became pallid, limp and lethargic. The skin of her face, chest and legs was mottled. Her respirations and heart rate became rapid. She developed a slight cough and salivated excessively. She was placed in an oxygen tent and was given 3 1-minim doses of adrenalin over a 15 to 20 min. period. She improved rapidly thereafter except for persistence for several hours of lethargy and poor responsiveness. This reaction may have been allergic or it may have been due to accidental intravenous injection. The infant had received similar injections daily for the preceding 26 days with no untoward reaction whatsoever.

Therefore, further animal experiments with intravenous procaine penicillin in aqueous dispersion seemed indicated. Three albino rabbits weighing 2 to 3 kg. each were given procaine penicillin in water with Na-carboxymethylcellulose 0.5 ml. intravenously. All became prostrate after the injection; two had mild convulsions; all were partially recovered and on their feet five minutes after the injection. When 1.0 ml. was given, two of three rabbits died within two minutes. The third became prostrate with labored respiration but recovered.

When procaine penicillin in sesame oil 0.5 ml. was given intravenously to three such rabbits, two had mild convulsions, became prostrate with rapid respiration, but recovered. When 1.0 ml. was given, all the three rabbits had tonic convulsions followed by prostration. One died within 15 minutes after injection and a second apparently recovered but was found dead the following morning. The third survived. Autopsies on the two that died showed fat embolism in the lungs and kidney, pulmonary edema and congestion and central necrosis of the liver.‡

It would appear, therefore, that every precaution should be taken with either of these preparations to avoid intravenous injection.

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* The results given here were obtained with crysticillin®, supplied by Dr. H. S. Newcomer, E. R. Squibb & Co., New York City. Subsequently, similar results were obtained on 12 patients with this dosage using the same type of preparation, duracillin®, "For Aqueous Injection," supplied by Dr. Raymond M. Rice, Eli Lilly & Co., Indianapolis.

† This patient was on the private service of Dr. Ralph Spaeth, to whom the authors are indebted for permission to study and report this incident.

‡ The authors are indebted to Drs. C. G. Weigand and F. C. Ottati of the Lilly Research Laboratories, Eli Lilly & Company, Indianapolis, for the data on rabbits.

Discussion

When procaine penicillin G in sesame oil 4000 u./lb. body weight was given to infants and children weighing between 4.5 and 18.0 kg., 35% of the subjects had less than 0.04 u./ml. at the end of 24 hours. With the same dosage of K penicillin G in peanut oil and beeswax (new Romansky formula), only 6% had less than 0.04 u./ml. at the end of 24 hours. However, when procaine penicillin G in sesame oil 8000 u./lb. body weight was given, all the subjects had 0.04 u./ml. or higher in their serum at the end of 24 hours.

When 8000 u./lb. body weight of each of the three different procaine penicillin preparations described in this report were given, no significant differences were noted in the serum penicillin concentrations 24 hours after administration. The averages of the logarithms of the serum penicillin levels (or the anti-logs) are nearly alike with the three preparations, and the distributions of the logarithms are similar.

The choice between these preparations, therefore, rests on criteria other than the serum penicillin concentrations. The aqueous preparation offers a distinct advantage in that both sesame oil and peanut oil are eliminated. Particularly with the elimination of peanut oil, the rate of untoward reactions is reduced.[17] In addition the use of the aqueous preparation eliminates the need for dry syringes. The same care, however, should be exercised to avoid intravenous administration of the aqueous preparations as with those containing oil.

A dosage of 8000 u./lb. every 24 hours for infants and children weighing between 4.5 and 18.0 kg. is suggested for mild infections, particularly those due to the more susceptible bacteria (i.e., those inhibited in vitro by 0.04 u./ml. or less). Using preparations containing 300,000 u./ml., a practical schedule of dosage would be 0.25 ml. for a 4.5 kg. infant, 0.5 ml. for a 9.0 kg., 0.75 ml. for a 13.5 kg. and 1.0 for an 18.0 kg. child. It is suggested that this dosage be given every 12 hours for serious infections, particularly those due to relatively more resistant bacteria (e.g., those inhibited in vitro only by 0.40 u./ml. or more).

Summary

Table I summarizes most of the pertinent data in this report on the serum penicillin concentrations 12 and 24 hours after intramuscular injection of K penicillin G in peanut oil and beeswax, which is fluid at room temperature, and of three different procaine penicillin preparations. These three preparations are procaine penicillin G in sesame oil, procaine penicillin G in peanut oil with 2% aluminum monostearate, and procaine penicillin G in water with Na-carboxymethylcellulose. When they were given in a dosage of 8000 u./lb. to infants and children, weighing between 4.5 and 18.0 kg., there was no statistically significant difference in the serum levels obtained. A dosage schedule for these preparations is suggested for pediatric use. The aqueous preparation offers some advantages which are discussed. Experiences are reported which emphasize the necessity of avoiding intravenous administration of all these preparations.

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SPANISH ABSTRACT

Estudios de Penicilina en Pediatría: III. Penicilina G Procaina en Aceite de Sésamo, en Aceite de Cacahuete con 2% Aluminum Monostearate y en Agua con Carboximetilceluloso de Sodio

Este informe hace un resumen de la mayor parte de los datos pertinentes a las concentrados de penicilina de suero 12 y 24 horas después de la inyección intramuscular de K-penicilina G en aceite de cacahuete y cera de abeja, la que es flúida a la temperatura de cuarto, y de las tres preparaciones diferentes de penicilina procaina. Estas tres preparaciones son penicilina G procaina en aceite de sésamo, penicilina G procaina en aceite de cacahuete con 2% aluminum monostearate, y penicilina G procaina en agua con Na-carboximetilceluloso. Cuando se dieron en una dosis de 8000 u./lb. a infantes y niños que pesaban entre 4.5 y 18.0 kg., no hubo diferencia estadisticamente signifivativa en las cantidades de suero obtenidas. Para uso pediátrico se sugiere un horario de dosis para estas preparaciones. La preparación acuosa ofrece algunas ventajas que son discutidas. Se reportan experiencias que marcan la necesidad de evitar administración intravenosa de todas estas preparaciones.

29th and Ellis Avenue

CHRONIC POISONING DUE TO EXCESS OF VITAMIN A

Description of the Clinical and Roentgen Manifestations in Seven Infants and Young Children

By JOHN CAFFEY, M.D.
New York City

DURING 1945 the author observed a girl 25 months of age who had cortical hyperostoses in many sites of the skeleton. Her disease began when she was 19 months of age. She was described as a probable example of infantile cortical hyperostosis,[1] although at that time there was some question of the validity of including, in the syndrome of infantile cortical hyperostosis, patients such as this one who exhibited neither facial swellings nor mandibular hyperostoses and in whom the onset appeared after the first four months of life. Later it was learned that this patient had been taking one teaspoonful of oleum percomorphum daily for "several months" before the symptoms appeared. The author now has records of seven patients who ingested excessive amounts of vitamin concentrate A and D over long periods and who present similar clinical, roentgenographic and chemical findings. The subject of this report is a description of the toxic signs and symptoms in this group. The morbid anatomy of the lesions is unknown; there have been no biopsies or necropsies.

CASE REPORTS

Case 1. A. M., a girl 25 mo. of age, had complained of anorexia for 6 mo. and pain in the legs for 4 mo. She had been well until the 19th mo. when she became fussy, tired easily and began to refuse most of the food offered. During the 21st mo. the left shank and foot became swollen and painful; she refused to walk and the left shoe could not be worn because the foot was too large and tender. On several occasions she had heavy sweats at night.

Physical examination disclosed malnutrition, dry cracked lips, bilateral palpable clavicular swellings, and a tender firm swelling in front of the left tibia. These swellings were all deep, firm, not overly warm, not discolored and unattached to the skin. There was a similar swelling in the left foot. She refused to stand or to walk. Liver was not enlarged to palpation. She was and remained afebrile.

Hemogram and urinary examinations were normal. Blood proteins were present in normal concentrations (albumin 4.6 gm., globulin 2.3 gm./100 cc.), as were the serum calcium and phosphorus (10.6 mg. and 4.3 mg./100 cc., respectively). Blood NPN was 34 mg./100 cc. Serum phosphatase activity equaled 18 Bodansky units. ESR was 22 mm. in 1 hr. (Westergren). Blood serum gave a nonsyphilitic reaction to Kline's test. No serum agglutinins for the typhoid-dysentery-cholera group of bacteria were found in dilutions of 1:20 or higher.

Roentgen examination of the skeleton revealed cortical hyperostoses in both clavicles, in the right and left 7th ribs, both ulnas, right femur, left tibia, right fibula, and in all of the metatarsals in both feet, save the 1st metatarsals (Fig. 1). The mandible and the cranium were normal roentgenographically. There were no destructive changes anywhere in the skeleton and the bones unaffected by hyperostosis were all normal. Maturation of the skeleton was normal.

From the Department of Pediatrics, College of Physicians and Surgeons, Columbia University, and the Babies Hospital, New York City.

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The course in the hospital was striking. At first all food was refused and the patient was inactive, apparently from painful pseudoparalysis associated with the tender swellings in the legs and feet. After a few days she was feeding herself and taking a normal diet in normal amounts. At the end of about 4 days, most of the pain and tenderness had subsided although the swellings persisted. A bone biopsy had been planned but this was cancelled owing to the rapidity of recovery.

During the 2nd wk. of hospital residence it was learned from the mother that she had voluntarily increased the dose of oleum percomorphum* several months before so that the child had been receiving daily approximately 150,000 u. vitamin A and 22,000 u. vitamin D. This dosage had been stopped on admission to the hospital and clinical improvement was almost immediate.

After 22 days of hospital residence the patient was discharged asymptomatic. In roentgen films made 3 mo. following discharge, the hyperostoses were still visible but were all smaller and more sclerotic than before. One year later the hyperostoses were invisible roentgenographically. She has had no recurrence of symptoms for 4 yr.

Case 2. B. K., a girl, was 21 mo. of age when she was first seen in consultation with her pediatrician who had made a diagnosis of infantile cortical hyperostosis. She had been well until the 19th mo. when she became restless and "whiny" and a painful tender lump appeared on her right shin. For 3 wk. she had been refusing food and was unwilling to walk. Penicillin intramuscularly did not modify these manifestations. At the same time she became hyperirritable; insomnia was marked and she sweated excessively at night. She screamed when the weight of the bed clothes was on her, and resisted attempts to dress her, put on her shoes or change the diaper. Two weeks before, tender swellings first made their appearance in the left forearm and on the dorsum of the right foot. One week prior to the consultation a large hard lump appeared over the occiput but there were no facial or mandibular swellings. The temperature never exceeded 37.8°C.

In the physical examination the 21st mo., she was found to be exceedingly irritable and apprehensive of being touched. Photographs and roentgen films were made with great difficulty. The lips, especially the lower lip, were dry and cracked. Deep, firm, tender swellings were visible and palpable in the occipital region, in both forearms, on the ventral surface of the right shank, and in the lateral aspects of the dorsum of both feet (Fig. 2A and B). Liver was not enlarged and temperature was normal.

Hemogram and urinary findings were normal. ESR was 24 mm. after 1 hr. Multiple cortical hyperostoses were demonstrated by roentgenographic examination in both ulnas, left tibia and in both 5th metatarsals (Fig. 2C, D and E). Mandible was normal and there was no sign of bone production under the large swelling in the occipital region. The mother on being questioned in more detail about vitamin intake related that she had been giving the patient 1 teaspoonful of oleum percomorphum daily since the 12th mo. of life, which meant that this child had received 200,000 to 300,000 u. vitamin A daily over a period of about 9 mo. Blood withdrawn at this time showed a concentration of 330 u. of vitamin A/100 cc. plasma (normal 50-150); blood carotene was 70 gammas/100 cc. (normal 40-200 gammas).

Oleum percomorphum was stopped and within 4 days the patient was asymptomatic, although swellings were still present. She began to take normal amounts of food; the pain, tenderness and hyperirritability disappeared completely and sleep was undisturbed. The swellings gradually diminished in size so that they could not be detected after about 2 wk. In films, the hyperostoses in the 5th metatarsals were barely visible at the end of 6 wk. although, at the same time, the ulnar and tibial hyperostoses were only slightly diminished in size and much denser than earlier. At the end of 1 yr., all the hyperostoses were invisible save slight residual thickening in the cortical walls of the ulnas and the right tibia. The patient has thrived during the last 23 mo.

Case 3. H. A., a boy 12 mo. of age, was referred for roentgenographic examination with the clinical problem of soreness of the left shoulder and swelling and failure to use the left arm. These symptoms had been present for approximately 3 wk. The referring pediatrician suspected unrecognized traumatic injury to the left shoulder joint. There were no constitutional symptoms; the appetite had remained good and there had been no fever.

Roentgenographic examination disclosed ulnar hyperostoses (Fig. 3). Remainder of the skeleton,

* Oleum percomorphum (Mead Johnson) is made up of liver oils of the percomorph fishes, viosterol and other fish oils. It is standardized to contain not less than 60,000 u. vitamin A and 8,500 u. vitamin D/gm.

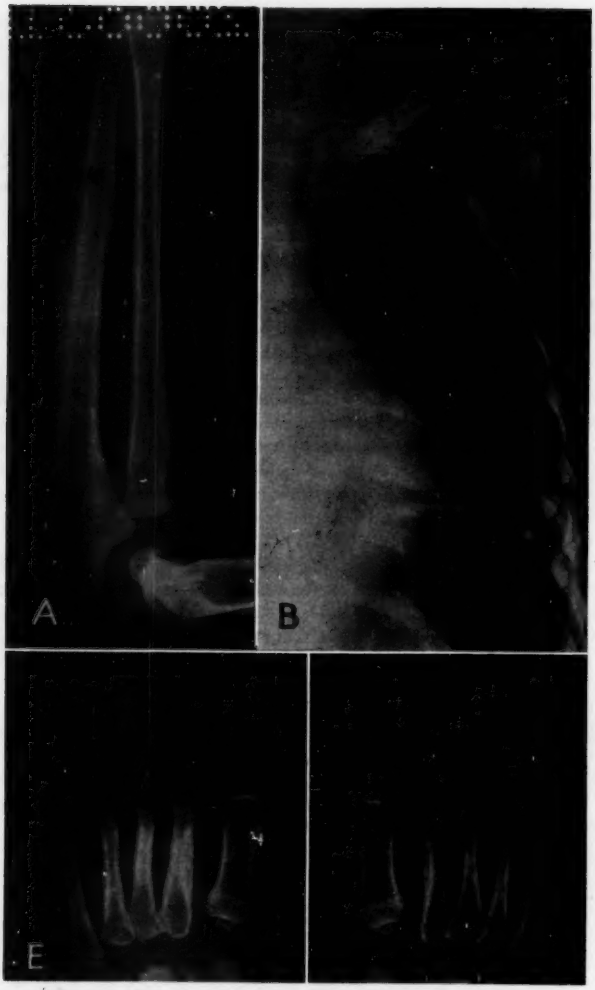

FIG. 1 (Case 1). Legend on page 675.

including the mandible and bones of the feet, were normal roentgenographically at this time. A presumptive roentgen diagnosis of hypervitaminosis A was made on the basis of the symmetric ulnar hyperostoses and, on direct questioning, the father stated that the infant had been receiving 2 teaspoonfuls of oleum percomorphum daily during the preceding 6 mo. (400,000 to 600,000 u. vitamin A/day). The family pediatrician later reported that the mistake in dosage was due to error in purchase at the drug store. The mother had supposed she was getting cod liver oil and the druggist was under the impression that she ordered oleum percomorphum.

Infant was well nourished, without pallor or fever. There were many large and small patches of erythema in the skin and in these areas numerous scratch marks were present. Pruritus had not been recognized by the parents. In the left forearm there was a long, poorly defined, firm tender swelling which was not discolored or overly warm. Liver was not enlarged.

Blood count and urinary findings were normal. ESR was 24 mm. after 1 hr. Serum calcium was 9.9

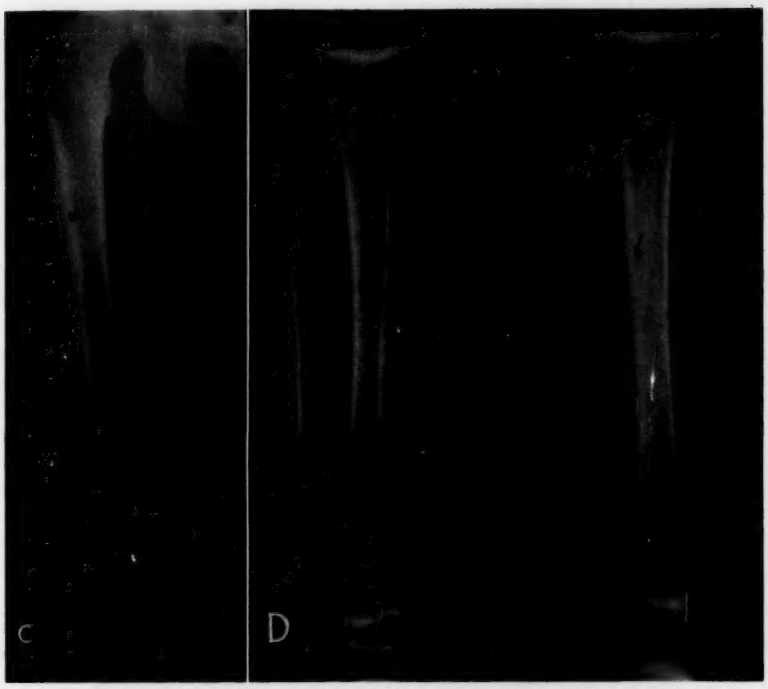

FIG. 1 (Case 1). Multiple cortical hyperostoses in A. ulna; B. L. clavicle and L. 7th rib; C. R. femur; D. L. tibia and R. fibula; E. 2nd, 3rd, 4th and 5th metatarsals in both feet. First metatarsals are not affected.

mg./100 cc.; phosphorus 4.8 mg./100 cc.; serum phosphatase activity equaled 15.2 Bodansky u. Kline's test on blood serum gave a nonsyphilitic reaction. Concentration of vitamin A in blood plasma was 1384 I.U./100 cc. (normal 50-150); total blood lipid was 840 mg./100 cc.; blood carotene concentration equaled 146 gammas/100 cc. (normal 40-200).

The ingestion of vitamin concentrate was stopped and pain and tenderness in the left arm disappeared after 4 days. The patient has remained asymptomatic. In films of the skeleton made 10 wk. later, the ulnar hyperostoses were still visible but were smaller and more sclerotic; in films of the feet, symmetric hyperostoses of the 2nd metatarsals were now visible although they had not been visible in the earlier films and the patient had never had signs or symptoms in the feet.

Case 4 (Dr. A. Ashley Weech, Children's Hospital, Cincinnati). W. K., a boy, was first seen at 32 mo. of age when he complained of painful feet of 3 wk. duration. Twelve days before, tender swellings appeared in the left hand, left arm and left shin. He became generally irritable but had no fever and retained a normal appetite. During the 10 days prior to admission, there had been several nosebleeds. On admission the parents stated that he had been receiving 2 teaspoonfuls of cod liver oil daily.

The boy was well nourished and mentally alert. Liver edge was at the costal margin. In the left forearm there was a long, hard, tender swelling over the ulna. The swelling was not overly warm or discolored. There were similar swellings on the left thumb, over the left 2nd metacarpal and over the left tibia. Regional lymph nodes were not enlarged. Both feet and one wrist were also slightly swollen. There was no reaction of the skin to tuberculin or histoplasmin.

Findings in the blood count and urine were normal. Kahn's test on the blood gave a nonsyphilitic reaction. Serum calcium was 10.7 mg./100 cc.; phosphorus 4.8 mg./100 cc.; serum phosphatase activity equaled 19 Bodansky u. Blood protein nitrogen was 30 mg./100 cc.

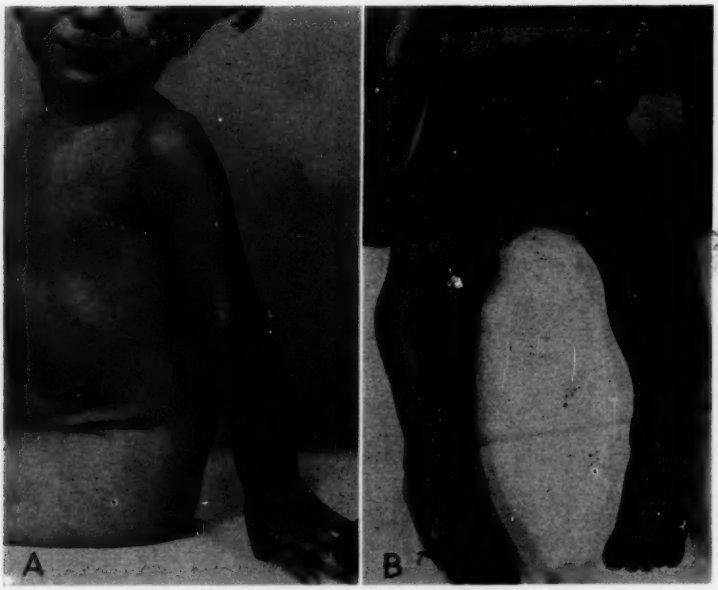

FIG. 2 (Case 2). Legend on page 677.

Roentgenographic examination of the skeleton disclosed hyperostoses in the 2nd left metacarpal (Fig. 4), both ulnas, both tibias and the fibula. In the feet both 4th metatarsals were thickened. The bones of the head and chest were normal roentgenographically and maturation of the skeleton was normal.

The course in hospital was uneventful. Before discharge it was learned that the mother had been giving the child oleum percomorphum instead of cod liver oil. Three years later the history was reviewed again with the mother. In review she stated that 10 drops of oleum percomorphum® were given daily from the 6th wk. until the 17th mo. of life. During the 17th mo., the child had a severe laryngotracheitis and the mother, deciding that more vitamins would be beneficial, increased the dose to 1 teaspoonful of oleum percomorphum daily. This dose had been continued during the 15 mo. which preceded admission to hospital.

Case 5 (Drs. S. Z. Levine and John Dale, Jr., New York Hospital, New York City). A. C., a boy 18½ mo. of age, was admitted with a chief complaint of pain in the bones of a few weeks' duration. Appetite had always been poor. Drisdol® with vitamin A,* a vitamin concentrate of A and D, had been started at 1 wk. of age when a "dropper-full" was given daily. After the 12th mo., the vitamin concentrate was increased to ½ and later ¾ teaspoonful daily, which provided about 125,000 u. vitamin A and 20,000 u. vitamin D. After the 13th mo., 1 teaspoonful of drisdol® with vitamin A (about 250,000 u. vitamin A and 40,000 u. vitamin D) was given daily. Two weeks before admission he was said to have bruised his leg in a fall and had had pain in his legs.

Examination disclosed that he was hyperirritable and afebrile. Both hands were swollen and tender. Liver edge was 2 cm. below the right costal margin. Left shank and both forearms were swollen and tender.

Hemogram and urinary findings were normal. ESR was 27 mm. after 1 hr. Serum calcium was 10.5 mg./100 cc.; serum phosphorus 3.6 mg./100 cc.; serum phosphatase activity equaled 9.7 Bodansky u. Vitamin A concentration in the blood plasma was 1395 u./100 cc. (normal 80-200); blood carotene was 73 gammas (normal 50). Vitamin C content of the leucocytes was 4.2 mg./100 cc. (low). The Mazzini blood test gave a nonsyphilitic reaction.

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* Drisdol® with vitamin A is a solution in sesame oil of drisdol, vitamin D2 from ergosterol, and natural fish liver oils. Each gram contains 50,000 u. U.S.P. vitamin A and 10,000 u. vitamin D.

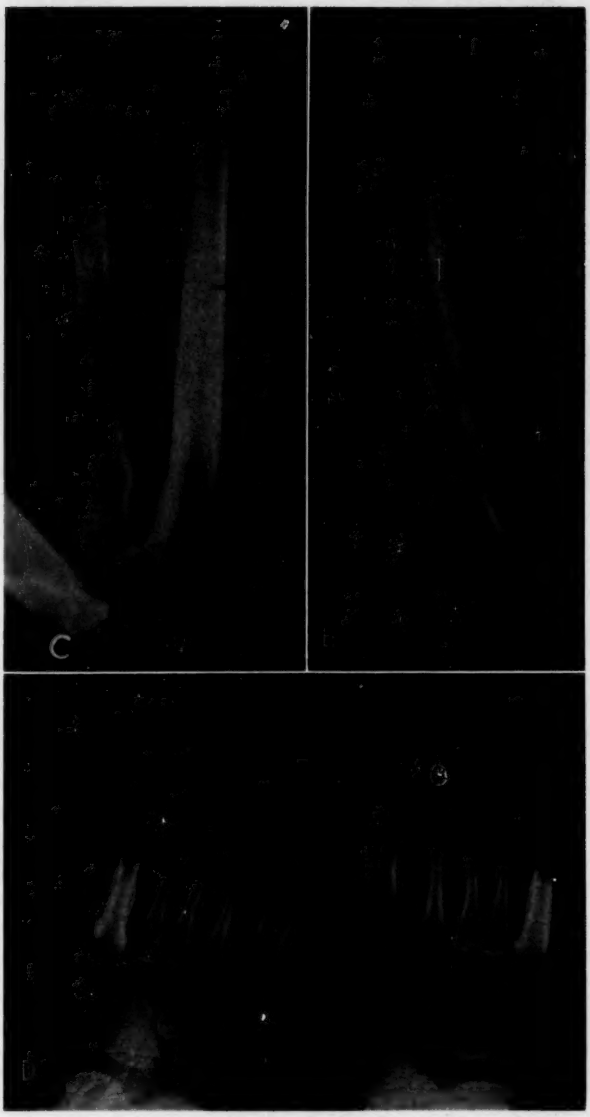

FIG. 2 (Case 2). Tender swellings and hyperostoses after 9 mo. of ingestion of excessive amounts of oleum percomorphum®. A. Ulnar swellings in forearms and fissuring of lips; B. symmetric swellings over 5th metatarsals and over R. tibia; C. long wavy cortical hyperostosis of ulna; D. symmetric thickenings of cortices of 5th metatarsals; E. long wavy cortical hyperostosis of R. tibia; striking absence of metaphyseal and epiphyseal changes.

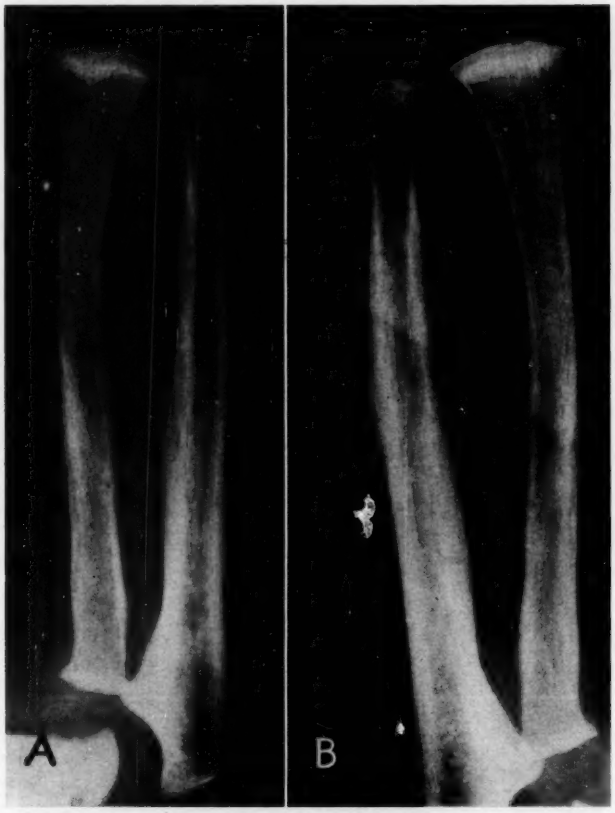

FIG. 3 (Case 3). Bilateral ulnar hyperostoses, 3 wk. after onset of soreness in arms, and after 12 mo. of intake of 2 teaspoonfuls of oleum percomorphum daily. Remainder of skeleton was normal roentgenographically, including feet. However, 10 wk. later and 10 wk. after oleum percomorphum had been stopped, symmetric hyperostoses of 2nd metatarsals were demonstrated roentgenographically.

Roentgenographic examination of the skeleton disclosed cortical hyperostoses in both clavicles, 6th and 7th right ribs, both ulnas, right radius, left tibia, right fibula, 4th and 5th right metatarsals and both 4th metacarpals (Fig. 5). Mandible was normal, as was skeletal maturation.

In the hospital the daily vitamin intake was reduced to approximately 12,000 u. vitamin A, 1,800 u. of D and 50 mg. ascorbic acid. Clinical recovery was rapid. He became active and asymptomatic; after 6 wk., he had gained 0.5 kg. The plasma concentration of vitamin A fell to 700 I.U. on the 12th hospital day, 500 I.U. on the 20th hospital day, 400 I.U. on the 27th day and 360 I.U. on the 37th hospital day.

Case 6. R. B., a boy 24 mo. of age, complained of pain, tenderness and swellings of the extremities for about 2 mo. According to his mother, he had always been in good health prior to the present complaints and had been taking the "usual" amounts of vitamin concentrates. The first symptoms were pain and swellings in the forearms, especially on the right side. One month later his shanks and ankles became swollen. At this time roentgenographic examination had shown symmetric hyperostoses in the ulnas. The feet and ankles became so swollen and tender that he could not wear his shoes. Immediate roentgenographic examination then disclosed no abnormal changes in the bones of the feet

FIG. 4 (Case 4). Cortical thickenings of 2nd metacarpal 3 wk. after appearance of tender swellings in hand. This patient had received 1 teaspoonful of oleum percomorphum daily for 15 mo.

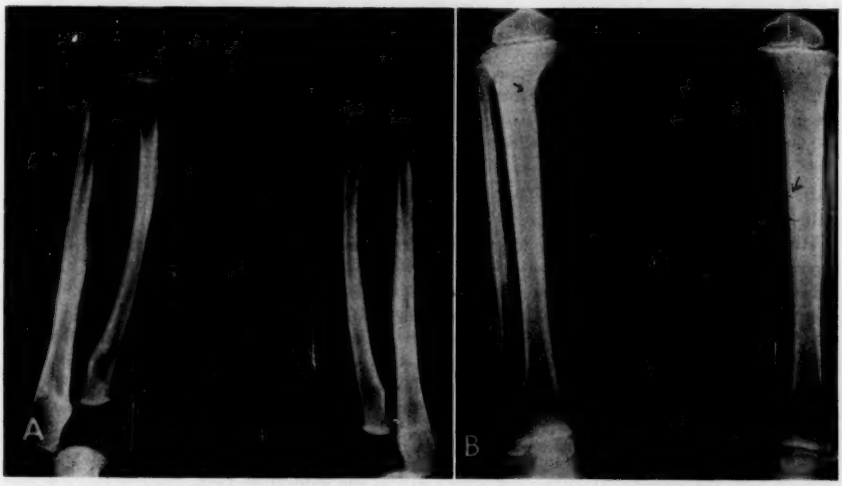

FIG. 5 (Case 5). Multiple cortical hyperostoses after 10 mo. of ingestion of excessive amounts of drisdol® with vitamin A, ½ to ¾ teaspoonful daily: A. in both ulnas and one radius. B. in L. tibia and R. fibula; arrow on right points to cortical defect not related to hypervitaminosis A.

or shanks. During the first weeks of the illness, fever occurred for short periods and then disappeared completely.

When examined by the author 2 mo. after onset, there were no abnormal physical signs. The swellings could not be identified clinically. In the roentgenographic examination, however, cortical thickenings were visible in both ulnas and in the 5th metatarsal (Fig. 6).

The family was requestioned 2 yr. later and it was then learned that the mother, who had given the original history, had had little to do with the care of the child during his 1st 2 yr. Actually he had lived with and been under the care of his grandmother. She stated that oleum percomorphum had been given daily since the first weeks of life, starting with a few drops daily with gradual in-

FIG. 6 (Case 6). Lamellated cortical hyperostosis of L. 5th metatarsal 9 mo. after beginning ingestion of ½ teaspoonful of oleum percomorphum daily. Two ulnas were only other bones affected.

FIG. 7 (Case 7). Symmetric, bilateral thin hyperostoses of ulnas after 15 mo. of ingestion of excessive amounts of navitol® in daily dosage of 1 teaspoonful, which provided approximately 200,000 u. vitamin A daily. Both clavicles were also thickened.

creases to ½ teaspoon daily. During the 7 mo. prior to onset of symptoms, the boy received approximately 100,000 u. vitamin A every day.

After a few days of hospital residence, the patient went to live with his mother and remained permanently asymptomatic.

Case 7 (Dr. Frederic N. Silverman, Children's Hospital, Cincinnati). R. B., a boy 37 mo. of age, had had a pruritic rash on his buttocks and back for 5 mo. His arms and legs had been tender for 2 mo. He frequently limped and refused to bend over owing to pain. He had been afebrile. His skin was dry and contained many scratch marks. The liver edge was 3 cm. below the right costal margin. He whined with pain when manual pressure was made on his legs and arms, especially when deep palpation was attempted. Blood count disclosed a mild anemia; there were 9 thousand leucocytes/cmm. with normal differential count. Serum calcium was 10.8 mg./100 cc.; serum phosphorus 5.2 mg./100 cc.; phosphatase activity of the serum equaled 22 Bodansky u. Roentgenographic examination of the skeleton disclosed cortical hyperostoses in both clavicles and both ulnas (Fig. 7). The bones of the feet were not filmed.

The cause of these clinical manifestations and roentgen changes remained unexplained until 4 yr. later when the mother was requestioned concerning the patient's intake of vitamin concentrates. The mother referred to the written records in her baby book and then stated for the first time that

navitol®,* a concentrate of vitamins A and D, had been started on the 10th day of life and 10 drops daily had been given until the 20th mo. During the 20th mo., the child suffered from a respiratory infection and the mother increased the dosage of navitol® to 1 teaspoonful daily (200,000 to 300,000 u. daily vitamin A). This excessive intake had been continued for 17 mo. prior to admission to the hospital. The patient recovered quickly in the hospital and has remained well for the ensuing 4 yr.

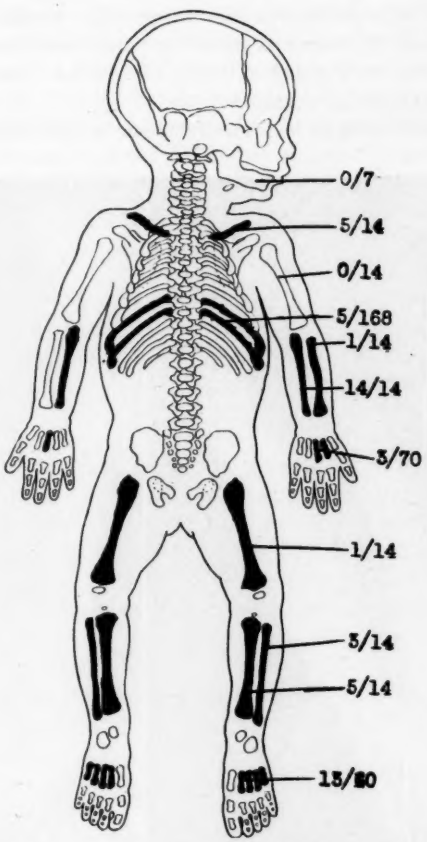

FIG. 8. Distribution of hyperostoses in 7 patients. Shaded bones were hyperostotic and numbers opposite each shaded bone indicate total number of such affected bones in all 7 patients on both sides of body. In every patient both ulnas were thickened and in every patient some of metatarsals were affected. First metatarsals, however, were not affected in any patient.

COMMENT

Acute poisoning due to the ingestion of large single doses of vitamin A is rare but has occurred occasionally when children have swallowed an entire (50 cc.) bottle of oleum percomorphum.[2] Under these circumstances, the only clinical manifestations have been transient nausea and vomiting. The toxicity of polar bear liver to Arctic travellers, Eskimos,

* A fish liver concentrate containing 65,000 u. U.S.P. vitamin A and 13,000 u. U.S.P. vitamin D/gm.

and their dogs has long been recognized; apparently it is due to the high content of vitamin A. Poisoning from this source is said to be characterized by headache and hyperirritability during the first 24 hours, followed by an irresistible desire to sleep. Desquamation of the skin begins at the mucocutaneous junctions of the lips during the second 24 hours, with rapid spreading until the entire skin peels in a few days. Several parties of Arctic explorers have been poisoned in this fashion and a number of deaths have been reported. Rodahl[3] found the vitamin A content in polar bear liver approximated 18,000 u./gm. He estimated that the ingestion of 0.5 kg. of polar bear liver represented an intake of approximately 8,000,000 u. of vitamin A.

Moore[3] found a wide variety of toxic manifestations in experimental vitamin A poison-

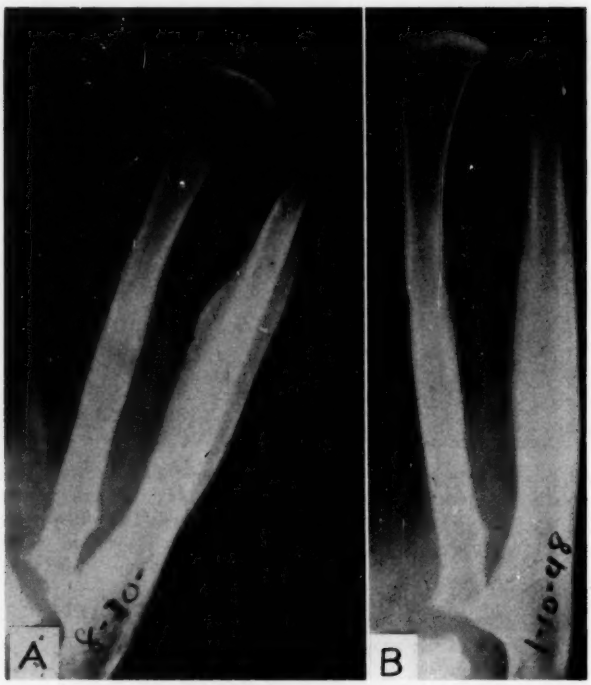

FIG. 9. Healing of ulnar hyperostosis in Case 2. A. Thin, wavy, shell-like cortical thickening during active phase of poisoning at admission. B. Four months after stoppage of vitamin concentrate; same hyperostosis is shrunken, smooth and more sclerotic.

ing in small animals. He observed roughening of the hair, alopecia, generalized seborrhea, enteritis, pneumonia, emaciation, softening and fractures of the long bones, and sudden profuse internal hemorrhage. Wolbach[4] and Maddoch, Wolbach and Maddoch[5] made comprehensive studies of the skeletal changes produced by excess vitamin A in small animals. They report that all features of skeletal maturation are accelerated: endochondral bone formation and subperiosteal appositional growth of the cortex. The rapid and excessive tubulation of rat bones resulted in tubular bones of smaller caliber than normal, in contrast to the swollen thickened shafts which have been observed in all the human examples of clinical vitamin A poisoning. Many of Wolbach's animals, especially the

younger growing ones, developed fractures after 6 to 10 days of high intake of vitamin A.

There are five examples of chronic vitamin A poisoning in infants and younger children reported in the literature. Josephs[6] first pointed out the dangers of high vitamin A intake in pediatric prophylactic practice and first demonstrated the value of the increased blood content of vitamin A in diagnosis of its poisoning. He described hypervitaminosis A in a boy 34 months of age who had received one teaspoonful of halibut liver oil (240,000 u. vitamin A) daily after the third month of life and occasionally drank the oil directly from the bottle. Toomey and Morrisette[7] first observed deep, hard, tender swellings in the extremities and were the first to describe cortical thickenings in tubular bones. Their patient was a boy 23 months of age who received one teaspoonful of oleum percomorphum daily from the second week until the 19th month and two teaspoonfuls from the 19th month until the 23rd month. After stoppage of oleum percomorphum and subsidence of clinical signs, Toomey and Morrisette reinduced the clinical signs by refeeding oleum percomorphum, and then a second time by feeding pure vitamin A.

Dickey and Bradley[8] reported tender swellings and cortical hyperostoses in a child 22 months of age who was poisoned by navitol® fed in daily dosage of three teaspoonfuls. Two patients of Rothman and Leon,[9] who were poisoned by excessive dosage of oleum percomorphum, exhibited tender swellings, cortical hyperostoses and high blood content of vitamin A. In all recorded cases, with the exception of the case of Josephs, rapid recovery followed the stoppage of ingestion of vitamin concentrate containing vitamin A.

In the group of seven patients reported here, the principal toxic manifestations were similar to those previously described; the roentgenographic observations are more complete and more detailed than those in earlier reports. Data in 12 cases now provide the opportunity for a more complete presentation of the clinical picture and a better insight into the differential diagnosis. Current findings in a comparatively large number of patients also make possible a comparison of hypervitaminosis A and infantile cortical hyperostosis, a syndrome with which vitamin A poisoning has been confused. It seems certain now that the two older patients described in 1946 (Caffey,[1] cases 2 and 5) as examples of infantile cortical hyperostosis actually suffered from excess vitamin A.

In all these patients, the excessive intake of vitamin A was unknown to their pediatrician and was not recorded in the original hospital histories. In three cases the history of overdosage was not obtained until two, three and four years after discharge from the hospital. Customarily, in history-taking, the interest in vitamin intake is directed exclusively at insufficiency of intake and the question of excessive intake is not raised. If overdosage is to be detected early from the history, the actual frequency of feeding and amounts of vitamin concentrate fed, the method of measuring the amount and the preparation used must all be sought for in detail. Apparently it is not an uncommon practice for mothers to stop measuring vitamin concentrate accurately, drop by drop, soon after they start its use; to save time the estimated dosage is poured directly from the bottle into a teaspoon. Under these circumstances the error of estimate appears to be invariably in the direction of overdosage. In one of the cases, the mother stated that she had been giving 20 drops of oleum percomorphum daily but, on further questioning, revealed that she had not been measuring each dose; actually she had been feeding the infant one bottle of 50 cc. of oleum percomorphum each month. The infant had received 60 to 70 drops each day instead of the 20 drops daily originally stated. Knowledge of the frequency and the amount of vitamin concentrate purchased may be more informative than the mother's statement of the unmeasured daily dose. The physician must also make certain that informants, especially fathers and grandmothers, actually know the details

of vitamin feeding. The possibility of confusion between oleum percomorphum and cod liver oil at the time of purchase should also be borne in mind.

All these parents were wholly ignorant of the harmful effects in higher doses of the vitamin concentrates recommended to them in small doses for prophylaxis. The parental reasons for giving toxic doses are interesting and important. In one case, the mother simply decided that, if a small amount of the concentrate was good for the baby's bones, a larger amount would be better. One grandmother increased the dosage to make sure that she was doing a better job at prophylaxis than the mother had been doing. In two cases the reason for higher dosage was never satisfactorily explained; apparently these mothers, ignorant of potential dangers, increased dosage in the blind belief that plenty of vitamins would promote the health of their children. In two instances dosage was increased and then toxic doses were continued in the hope of combatting and preventing upper respiratory infections. In another case, not reported in this group, the mother stated that her infant had developed such a fondness for oleum percomorphum that she had to feed one teaspoonful daily to keep the baby satisfied. In another instance the mother was unwittingly feeding oleum percomorphum instead of cod liver oil.

The estimated daily intake for these patients varied from about 75,000 to about 500,000 u. vitamin A. The data in this regard are difficult to evaluate precisely. In some cases the actual dosage was underestimated by the mother. On the other hand, such factors as incomplete filling of the teaspoon, spillage during feeding and spitting out of some of the concentrate by the infant may well have lessened the actual intake and absorption in comparison with the amount fed, as stated in the history. It should be emphasized that in no case was overdosage due to erroneous advice by a physician or erroneous labelling of the bottle by the manufacturer. It is equally true, however, that in no case did a manufacturer's label state the harmful effects of overdosage nor had any mother been so advised by her pediatrician. This failure to point out clearly the dangers of excess feeding of vitamin concentrates is a serious error of omission and should be corrected.

There are several possible toxic elements in the concentrates of vitamins A and D in fish oils, which presumably might have been the toxic agents in these patients. Vitamin D is an unlikely toxic factor because it had been used clinically in considerably higher dosages without toxic effect; also when children have been poisoned by massive administration of vitamin D, they have not exhibited signs and symptoms like those in this group. According to Debré,[10] the toxic manifestations of vitamin D poisoning in children include anorexia, polydypsia, renal damage, increased blood urea and blood calcium, and extraskeletal calcifications. There are some toxic proteins in several types of fish liver, notably halibut liver; supposedly, even minute traces of the liver proteins are removed from fish liver oils in the current methods of their extraction and processing.[11] Toomey and Morrisette[7] performed the crucial clinical experiment of feeding excess of vitamin A to their patient and reproduced the clinical picture of hypervitaminosis A. These facts all indicate that the toxic component of the vitamin concentrate fed to our patients was vitamin A.

There are several characteristic features in the clinical picture. In all cases there was a long latent period of several months between the start of excessive dosage and the appearance of diagnostic clinical signs. The length of this latent period did not depend on the size of the overdose. The shortest latent period was six months; the longest was 15 months. The appearance of tender swellings has been used as the criterion for the

onset of the clinical disease. In some cases pruritus and anorexia preceded tender swellings by several weeks or months; anorexia and pruritus are so common in children who do not suffer from hypervitaminosis A that their significance in children poisoned by vitamin A is exceedingly difficult to evaluate from a causal standpoint. Since anorexia is a prominent feature of vitamin D poisoning, it is possible that vitamin D played a part in the causation of anorexia in these patients. In Case 3, however, appetite remained normal during a period of six months of excessive vitamin concentrate feeding and for three weeks after the appearance of tender swellings. Enlargement of the liver has been found by others in several patients; the liver was normal in size in all the patients examined personally.

Tender swellings, hyperirritability and limitation of motion all became evident at about the same time. Tender swellings were most common in the forearms but they were more conspicuous in the shanks and feet in some patients. Swellings were always deep and firmly attached to underlying structures, apparently the bones. The overlying skin in contrast was always freely movable over the deeper masses and was never edematous or discolored. Tenderness appeared to be moderate and local heat was not increased. All types of handling were feared and resisted. Large temporal and occipital swellings developed in two patients but the mandible and face were always normal in all patients. Lymph nodes, regional to the swellings, were not enlarged.

Hyperostoses in two or more of the long bones were identified roentgenographically in every patient; the distribution and frequency of involvement of different bones are shown in Figure 8. Hyperostoses were found under all of the soft tissue swellings which could be demonstrated clinically. All the 14 ulnas in seven patients were affected and in every patient one or more of the metatarsals were thickened. None of the 12 first metatarsals examined was involved. The high incidence of localization in the ulnas and metatarsals appears to be the most diagnostic feature of the skeletal lesions of poisoning due to excess vitamin A intake. In Case 3, metatarsal thickenings were not visible three weeks after onset when ulnar hyperostoses were demonstrated, but 10 weeks after the withdrawal of all vitamin A by mouth, both second metatarsals were found to be thickened. There is no satisfactory explanation for the high frequency in the ulnas and metatarsals; it is possible that trauma played some part in thickening these relatively exposed bones. The bones at the roots of the extremities, the femurs and humeruses, which are relatively well protected from trauma by heavy muscles were the least affected. Only one of the 14 femurs and none of the 14 humeruses showed cortical thickening. The mandibles and scapulas were normal in all patients. Five of 14 clavicles exhibited deep cortical hyperostoses.

The earliest roentgenographic observations were in Case 3 in which films showed cortical hyperostoses in the ulnas three weeks after the appearance of clinical swellings in the forearms. Early, the hyperostoses have a shell-like appearance with a zone of diminished density between the subperiosteal thin layer of bone and the external surface of the old cortex. After withdrawal of vitamin A this intermediate clear zone disappears; the hyperostoses then shrinks onto the old cortex and fuses with it (Fig. 9). These solid sclerotic cortical thickenings are in turn gradually resorbed from within but remain visible for many months after complete clinical recovery. During the reparative phase some of the hyperostoses became lamellated.

The amounts of vitamin A in the blood have been increased in all patients whose bloods have been tested. The concentrations varied from 400 to 2000 u./100 cc. It is not cer-

tain how early blood vitamin A rises, or whether it is elevated during the long latent period prior to the appearance of clinical manifestations; it is possible, however, that an excess of vitamin A in the blood might point to the diagnosis while the patient was still asymptomatic. Following the stoppage of ingestion of excessive vitamin concentrate, vitamin A levels in the blood fell gradually and did not return to normal levels for several weeks (Case 5; Toomey,[7] Dickey[8] and Rothman[9]).

The rapid and complete clinical recovery of these patients after the stoppage of overdosage is one of the most distinct and convincing features of the syndrome. In patients observed personally, tenderness, pain, hyperirritability and anorexia have disappeared completely within one week. Recovery is comparable to the recovery in scurvy following the administration of vitamin C. In Case 1, recovery was so rapid after admission to the hospital that a bone biopsy which had been scheduled was cancelled.

As mentioned earlier, hypervitaminosis A has been confused by the author with infantile cortical hyperostosis. Personal communications from several sources indicate that this continues to be a not infrequent diagnostic error. Actually there are but two features which are common to both disorders; cortical hyperostoses and tender soft tissue swellings. In contrast, there are several outstanding differences which readily identify hypervitaminosis A and infantile cortical hyperostosis as separate entities. Infantile cortical hyperostosis has always made its appearance during the first four months of life and in one case was present on the first day of life; in hypervitaminosis A, on the other hand, diagnostic clinical signs have never been recognized prior to the 12th month of life. It is interesting that there is no recorded example of onset between the 5th and 11th months in either disorder. The face and jaw have been swollen and the mandible has been thickened in every case of infantile cortical hyperostosis; these structures have not been affected in a single case of hypervitaminosis A. Metatarsal hyperostoses have been present in every case of vitamin A poisoning in which the feet have been examined roentgenographically but have been demonstrated in only one case of infantile cortical hyperostosis. The blood vitamin A has been increased in hypervitaminosis A in every patient tested; blood vitamin A levels were normal in the only six patients with infantile cortical hyperostosis so tested. Fever is the rule in infantile cortical hyperostosis (15 of 17 cases); fever, other than transient fever due to respiratory infection, was absent in all cases of hypervitaminosis A.

Excessive intake of vitamin concentrate A and D preceded poisoning by vitamin A in all cases; vitamin intake has apparently not been excessive in any cases of infantile cortical hyperostosis. Also the feeding of excessive vitamin concentrate A and D during the first four months of life has not produced the manifestations of infantile cortical hyperostosis.[6,7,9] It seems likely that impaired absorption of vitamin A in oil during early life[12] is responsible for the absence of toxic symptoms in babies fed large amounts of oleum percomorphum during the first months of life. Recovery from vitamin A poisoning is dramatically rapid after admission to hospital and stoppage of the excessive ingestion of vitamin A; in contrast, the signs and symptoms of infantile cortical hyperostosis have continued and exacerbations have occurred weeks and months after hospital entry when it was certain that there was no excessive ingestion of vitamin A. Scapular lesions are unknown in vitamin A poisoning; they have been present in several cases of infantile cortical hyperostosis. Soft tissue swellings in the latter disease are usually much larger and more tender and the edges of the hyperostoses are much rougher than their counterparts in hypervitaminosis A.

Summary and Conclusions

The clinical manifestations, the roentgenographic changes in the skeleton and the elevation of blood vitamin A are reported in a group of seven infants and younger children poisoned by ingestion of excessive quantities of vitamin concentrates A and D over periods of several months.

The differential features of vitamin A poisoning and infantile cortical hyperostosis are discussed.

Three types of vitamin concentrate A and D, commonly used in routine pediatric prophylaxis, were found to be toxic when ingested in sufficiently large quantities over sufficiently long periods. The minimal preclinical latent period of vitamin A poisoning was about six months and the minimal toxic daily dose was about 75,000 units.

Excessive dosage was due to overenthusiasm for vitamins and ignorance of the dangers of high vitamin intake.

The hazards of vitamin A poisoning from the routine prophylactic feeding of vitamin concentrates A and D to healthy infants and children on good diets are considerably greater than the hazards of vitamin A deficiency in healthy infants and children not fed vitamin concentrates.

Addendum

Since this manuscript was submitted for publication, two additional cases of vitamin A poisoning have been described (Fried, C. T., and Grand, M. J. H., Hypervitaminosis A, Am. J. Dis. Child. **79**:475, 1950). The clinical, chemical and roentgen findings are all similar to those in the other reports. A total of 14 cases of infantile and juvenile poisoning due to vitamin A have now been recorded.

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Spanish Abstract

Envenenamiento Crónico Debido al Exceso de Vitamina A: Descripción de Manifestaciones Clínicas y de Roentgen en Siete Infantes y Niños Menores

Las manifestaciones clínicas, cambios roentgenográficos en el esqueleto, y la elevación vitamina A de sangre se reportan en un grupo de 7 infantes y niños menores envenenados por la ingestión de cantidades excesivas de concentrados de vitamina A y D por períodos de varios meses.

Se discuten las características diferenciales del envenenamiento de vitamina A y la hiperostosis cortical infantil.

Se encontró que tres tipos de concentrados de vitamina A y D, comunmente usados en la rutina pediatrica profilaxis, son tóxicos cuando ingeridos en cantidades suficientemente grandes durante períodos suficientemente largos. El período latente preclínico mínimo de envenenamiento de vitamina A fué de 6 meses y la dosis diaria tóxica mínima fué de poco más o menos 75,000 unidades.

La dosis excesiva fué debida al gran entusiasmo por vitaminas y a la ignorancia de los peligros de alta toma de vitaminas.

Los peligros del envenenamiento de vitamina A de la alimentación profilactica de rutina de concentrados de vitamina A y D a infantes y niños sanos que tienen buenos dietas son considerablemente más grandes que los peligros de la deficiencia de vitamina A en infantes y niños sanos que no estan alimentados con concentrados de vitamina.

622 West 168th Street

CHRONIC ACIDOSIS OF RENAL ORIGIN IN INFANCY

By WESTON M. KELSEY, M.D., JOHN B. REINHART, M.D., AND JOHN FISHEL, B.S.
Winston-Salem, N.C.

NEWER concepts of renal physiology and pathology have permitted the recognition of syndromes caused by the failure of one or more of the specific renal tubular functions. The metabolic defects may be single as in renal glycosuria or there may be several defects as in the DeToni-Fanconi syndrome. The purpose of this report is to describe two infants who apparently were unable to reabsorb bicarbonate and had persistent severe acidosis with no evidence of parenchymatous renal disease. The renal defect in one patient disappeared; he has been well for three years. The other patient has done well for nine months on simple therapy. Only one other case (Hartmann[1]) exactly like these has been found in the literature in a search which has not been exhaustive.

These two children were similar. Both had anorexia, vomiting, constipation, failure to gain weight, and then the sudden onset of fever, signs of acidosis, and collapse. Physical findings in both were minimal. The acidosis in Case 1 was complicated by generalized sepsis with B. subtilis, but the acidosis persisted after the infection had cleared. The essential acid base studies were those of increased serum chloride and decreased plasma bicarbonate. In Case 2, the serum CO_2 content was found to be about 2.5 mEq. higher than the combining power on two occasions. In spite of the acidosis both excreted a persistently alkaline urine. Unfortunately, in Case 1 there is no record of the method of measurement of the urine pH. Except for suggestive evidence of nephrogenic diabetes insipidus in Case 2, there was no evidence of any other tubular defect. Both children responded dramatically to the administration of alkaline salts.

CASE REPORTS

Case 1. W. W.,* an 11 wk. old male infant, was admitted to the hospital because of signs of acidosis. Family history was irrelevant. The child weighed 4.2 kg. at birth. The neonatal period was uneventful except for mild impetigo. He took an evaporated milk formula fairly well for the 1st 6 wk. of life, but gained slowly, having regained his birth weight on the 5th wk. At 6 wk. of age, it was noted that he was not taking as much formula as he had previously. Several formula changes were made but without improvement in the feeding problem. His weight became stationary and there was moderate constipation. When 9 wk. old he began to have episodes of projectile vomiting. At that time barium studies revealed a normally functioning stomach and duodenum. He was taken to another doctor when 10 wk. old and received a transfusion because of a hemoglobin of 10.5 gm. Cereal was offered but was refused. At that time he refused most of his feedings and vomited when he did take them. On the day of admission the respirations became deep and rapid and he became drowsy.

Physical examination revealed a listless undernourished child who was only 0.1 kg. above birth weight. The temperature was 37.9°C. rectally. Measurements were within normal limits. There were no abnormal findings other than those of moderate dehydration and Kussmaul respirations. Laboratory studies revealed the presence of a B. subtilis septicemia and pyelitis. Details of the B. subtilis infection have been described elsewhere;[2] details of the blood chemistry and urinary findings are given in Table

From the Department of Pediatrics of the Bowman Gray School of Medicine of Wake Forest College, and the Pediatric Service of the North Carolina Baptist Hospital, Winston-Salem, N.C.
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TABLE I

CASE 1: W.A.W.

	Serum Concentrations			Urine		Wt.	Therapy*
Date	NPN mg. %	CO_2 Capacity mEq./l.	Chloride m.Eq./l.	Sp. Gr.	pH	kg.	cc. Na Lactate
7-31-45		3		1015	6.0	4.2	125 cc. Normal saline (p) 100 cc. M/6 Na lactate (p)
8- 1-45	33	3	109	1010	6.0	4.3	400 cc. M/6 Na lactate (p)
8- 2-45	33	14		1015	6.0	4.7	
8- 3-45		14.5	112			4.6	
8- 8-45		13		1015	7.5	4.8	
8-11-45		6.8				4.8	300 cc. M/6 Na lactate (p)
8-13-45		6	115.6	1010	7.5	4.8	250 cc. M/6 Na lactate (p)
8-15-45		9.5				5.0	30 cc. M/1 Na lactate (o) started 8-14-45
8-17-45		6		1012	7.5	5.0	100 cc. M/1 Na lactate (p)
8-19-45		12			Alk	5.0	100 cc. M/1 Na lactate (p)
8-21-45	33	7.7		1008	7.5	5.0	M/1 lactate decreased to 30 cc. 8-20-45 (o)
8-23-45		18.6			7.5	4.7	150 cc. M/6 Na lactate on 8-21; 8-22; 8-23; 8-24 (p)
8-27-45		12.2	112	1010	7.5	5.0	250 cc. M/6 Na lactate (p) 20 cc. 2M Na lactate (o)
8-29-45		19.4	106	1024	7.0	5.0	300 cc. M/6 Na lactate (p) 40 cc. 2M Na lactate (o)
8-31-45		13	96.4	1018	7.0	4.8	300 cc. M/6 Na lactate (p)
9-10-45		15					75 cc. 2M Na lactate (o)
9-25-45		14					75 cc. 2M Na lactate (o)
11- 5-45		18				6.8	Gradually decreased
7-17-46	39	15	96			10.2	None
7-29-47	36	18.4	99	Serum pH 7.46			None

* p = Parenteral o = Oral.

I. On one occasion the Ca was 8.1 mg. per cent and the P was 5.6 mg. per cent. No tests for urinary Ca excretion were done. At no time was there significant or persistent albuminuria, glycosuria or acetonuria. The specific gravity of the urine was usually 1.015 though on 2 occasions it rose to 1.018 and 1.024. In the hospital he did well on Na lactate orally. He improved at home and the lactate was gradually decreased until 1 yr. after admission he was able to get along with no therapy. For the past 3 yr. he has been completely well and has developed normally. No residual urinary changes have been found suggesting the presence of chronic pyelonephritis.

Case 2. F. P. was a 10 mo. old male at the time of admission to the hospital. Family history was irrelevant except that the parents were small. He weighed 2.8 kg. at birth and regained his birth weight on the 7th day. He was started on an evaporated milk formula when 3 days old and continued to take it well until the age of 3 mo. Cereals and fruit had been taken well since he was 1 mo. old. When he was 3 mo. old he started to take less formula and solids than he had before and he failed to gain weight. From the time he was 3 mo. old until he was 8 mo. old he rarely took more than 0.3 kg. of formula daily. When 8 mo. of age he began to take even less formula and vomited frequently. The vomiting became more severe. At 9 mo. he had a febrile episode said to be caused by tonsillitis. At that time he weighed 6.2 kg. Following this episode the mother noted that he had become thirsty and voided frequently. Constipation was marked. He had never had diarrhea. Two days prior to admission he had a high fever and vomited with every feeding. The family physician was unable to find a cause for the fever and referred the patient for further study. In spite of his difficulties he had developed normally and was able to pull himself to a standing position.

On admission he was an irritable small infant with considerable loss of subcutaneous tissue but with no definite loss of skin turgor. His length was 67.9 cm. with an upper to lower ratio of 1.43. The head measurered 44.4 cm. in circumference. The weight was 5.7 kg. The anterior fontanelle measured 1 x 1½ cm. No teeth had erupted. The only finding of interest was craniotabes. No cause was found for the temperature of 38.8°. Hemogram was within normal limits except for an elevated WBC count. Blood chemistry and urinary studies are shown in Table II. The serum pH was determined by the

method described by Kelsey and Leinbach.[3] The values are slightly higher than those usually accepted as normal and as a result will give a low pCO_2. The serum Ca was 11.6 mg. per cent and the P was 6.0 mg. per cent. The urinary Ca was within normal limits as measured by the Sulkowitch test. At no time was albumin or a reducing substance found in the urine. Urinary ketone bodies were absent at all times. The specific gravity of the urine remained between 1.010 and 1.015 at all times including the period when he was receiving pitressin tannate. Roentgenologic studies failed to show calcification in the kidneys and studies of the long bones showed no evidence of rickets or osteoporosis. The output of both urinary ammonia and titratable acid was low but the ratio was 1.4.

The course in the hospital was remarkable. The constipation was extreme and he became listless and developed abdominal distention when he failed to receive daily enemata, at which times hard feces were recovered. During his period of hospitalization he had several crises similar to one which occurred 5 days after admission. At that time he became listless and his color ashen. Rapid deep respirations were noted following which spasticity appeared. He perspired profusely and gradually failed to respond to any stimuli. Twelve hours after the administration of parenteral fluids he appeared

TABLE II

CASE 2: F.W.P.

Date	Serum Concentrations					Urine			Wt.	Therapy†
	NPN mg. %	Total Base mEq./l.	CO_2 Capacity mEq./l.	Chloride mEq./l.	pH	Sp. Gr.	pH	12 hr. Coll Cl_2 as NaCL	kg.	
1-12-49			7.7		7.33				5.0	250 cc. 5% glucose in normal saline (p)
										120 cc. M/6 Na lactate (p)
1-12-49		145.8	8.2	106	7.35		7			200 cc. 5% glucose in H_2O (p)
1-13-49		157	15.4	118	7.47				5.4	
1-15-49		152	12.2	109	7.48			Vol. 210 cc. 1.12 gm.	5.6	
1-26-49			16			1013	Alk		5.7	300 cc. 5% glucose in normal saline (p)
1-31-49			13.5				8		5.5	On 1-30-49 received 1800 cc. fluids
										200 cc. M/6 Na lactate (p)
2- 1-49	29	147.2	12.6	107.6	7.47		7		5.5	
2- 2-49		155	10.4	115.6					5.6	
2- 3-49	32	164	15.4*	129.5	7.45	1015	7.5	Vol. 225 cc. 2.03 gm.	5.6	
2- 5-49		164.8	13.5	119	7.5			1.31 gm.	5.6	Pitressin tannate I.M. 2-6-49 (p)
2- 8-49		144.8	11.3	111	7.32			Vol. 145 cc. 0.18 gm.	5.6	Pitressin tannate I.M.
2- 9-49		148.2	10.4	104	7.39	1010			5.7	Pitressin tannate I.M.
2-12-49		147.8	10.4	107.6	7.45		7		5.9	Pitressin tannate discontinued 2-11-49
2-14-49		146.9	13	104	7.44	1014		Vol. 172 cc. 0.464 gm.	5.7	$NaHCO_3$ 2.4 gm. on 2-15-49. Daily
2-17-49		145.8	10	108	7.39				6.0	$NaHCO_3$ 2.4 gm. (300 cc. M/6 Na lactate) (o)
2-18-49			18.5	107.6		1008		Vol. 485 cc. 1.78 gm.	6.2	$NaHCO_3$ 3.4 gm. (o)
2-19-49				102					6.2	$NaHCO_3$ 4.5 gm. (o)
2-21-49		145.4	10.4	101.5	7.43	1009	7.5		6.1	$NaHCO_3$ 4.5 gm. $NaHCO_3$ 9 gm. on 2-20-49 (o)
2-23-49		148.5	13		7.58				6.2	$NaHCO_3$ 9 gm. (o)
2-24-49			24		7.63				6.2	$NaHCO_3$ 6 gm. (o)
2-25-49		146	22	96	7.63				6.2	$NaHCO_3$ 4.8 gm. (o)
3- 4-49	30	145	17.6	98	7.55				6.2	$NaHCO_3$ 4.8 gm. (o)
3-25-49	25	148.2	20.3	100	7.56				6.6	$NaHCO_3$ 4.8 gm. (o)
4-28-49		143.7	15	99	7.54					$NaHCO_3$ 4.8 gm. (o)
5-16-49	44	148.2	12.6	103	7.46				6.9	$NaHCO_3$ discontinued on 5-12-49. Anorexia, listlessness prompted mother to start drug on 5-15-49.

* Determined as content.

† p = Parenteral o = Oral.

about as he had on admission. It was then noted that his intake of fluids was considerable, averaging about 1200 cc. daily. He voided frequently and copiously, sometimes as much as 21 times a day. When attempting to restrict fluids to see if he could concentrate the urine he went into collapse, and it was felt unwise to repeat this test. He was offered an increased intake of NaCl, but was unable to retain it. A trial on pitressin tannate failed to increase the specific gravity of the urine or alter the clinical course of the patient. Administration of Na lactate solution by mouth resulted in vomiting. He was then placed on Na bicarbonate by mouth and gradually improved. Constipation disappeared, vomiting stopped, appetite became ravenous and weight increased. There was definite decrease in the polydipsia and polyuria. He was discharged after 3 mo. in the hospital receiving 4.8 gm. of Na bicarbonate a day. This was taken without difficulty. The improvement continued 2 mo. until the bicarbonate was discontinued prior to re-evaluating his electrolyte status. Forty-eight hours after the bicarbonate was stopped he refused his feedings and then vomited. He became listless, thirsty, and appeared to the mother "as if he would die." She started the bicarbonate and by the time she was able to bring him back to the hospital he was greatly improved. More striking than any data were the mother's and neighbor's statements about the child's improvement on resuming the Na bicarbonate. Since that time he has continued to receive approximately 5 gm. of Na bicarbonate daily. There has been some variation in the CO_2 capacity, but it has always been lower than normal and therefore the medication has been continued. When last seen at 19 mo. of age, no physical abnormalities were present except that he was smaller than average. His CO_2 capacity was 16.7 mEq./1. His weight was 8.8 kg.

Discussion

From the limited evidence at hand it would appear that the chief metabolic defect in these patients was that of failure of reabsorption of bicarbonate. This conclusion was reached by ruling out other possibilities.

The chemical data in Case 2 suggest the possibility of a respiratory alkalosis. The serum pH by the method used indicated a systemic acidosis. No cases of respiratory alkalosis have been described in which over-ventilation has caused the CO_2 combining power to remain at such low levels for this long period of time. No clinical evidence of prolonged hyperventilation was present.

The possibility of a lesion producing abnormal loss of base was considered, but no site of such a loss could be found. He had no diarrhea or vomiting except after the onset of a crisis. Urinary excretion of Na could not be studied. The total base as determined by the conductivity method[4,5] remained within normal limits except during the periods when large amounts of parenteral fluids were administered. It is difficult to postulate a renal base losing lesion which permits the maintenance of normal serum base.

Increased reabsorption of chlorides could produce this syndrome. Little is known of the selective reabsorption of the chloride ion except in its relation to the Na ion and in the variations in response to changes in the CO_2 tension. The fact that the two patients had a drop in the blood serum chloride level following the administration of alkali salts suggests that the hyperchloremia was a compensatory rather than a primary mechanism. Neither patient had taken ammonium chloride or calcium chloride.

No defect in carbohydrate metabolism was found. The patients had normal blood sugar determinations and did not have ketonuria. It is recognized that it is possible to have ketonemia without ketonuria. This has been found in Von Gierke's disease, but these patients had no clinical evidence of that disturbance.

It seemed likely that the polydipsia and polyuria in Case 2 was of nephrogenic origin since pitressin tannate in amounts which control diabetes insipidus of central nervous system origin failed to alter the specific gravity of the urine or control the polyuria. Furthermore, though the intake and output were not measured accurately, the clinical cessation of the polyuria and polydipsia after correction of the acidosis suggests that the

polyuria was not a manifestation of primary failure of the tubules to reabsorb water. It is probable that this was caused in some manner by the abnormalities of the acid base balance.

The mechanism of the crises seen in these patients is not clear. The constipation was probably due to the excessive renal loss of water. The vomiting, anorexia and collapse could be similar to that seen in any form of acidosis and perhaps were associated with the effect of the low pH on the central nervous system. It is possible that they were due to hypokalemia as suggested by Albright and his co-workers.[6] This is speculation since neither serum potassium determinations nor electrocardiograms were done.

No explanation for the etiology of this syndrome can be made. Little is known about the reabsorption of bicarbonate in the proximal tubule.[7] The reabsorption in the distal tubule is probably a function of the activity of the carbonic anhydrase system.[8] The only known inhibitor of this system in clinical experience is sulfanilamide,[9] which these patients had not received.

It is recognized that substantiation of the hypothesis for the failure of reabsorption of bicarbonate is not proved, but it was impossible to carry out more detailed studies. It is felt that the clinical course of the patients supports the assumption that they were losing bicarbonate because of a renal defect, and there is little doubt that the recognition of this defect and institution of therapy resulted in a dramatic clinical remission.

Comparison with Other Types of Tubular Dysfunction

The only case exactly like Case 1 that could be found was Hartmann's.[1] As far as is known that patient recovered completely. The acid base picture presented by our patients is similar to that described by Rapoport.[10] The hyperchloremia and low alkali reserve in those patients was thought to be due to tubular dysfunction caused by extremes of dehydration. We have seen similar patients.[11]

The next group which comes closest to simulating those reported here are those of Butler, Wilson and Farber.[12] The symptoms and chemical findings corresponded to those of our patients, but in all of those renal calcification was found and death occurred by the age of one year. Case 1, reported here, would not fit into this group since he has been well for five years. Case 2 could fit into this group since one of the patients described by Butler et al.[12] had no calcification by roentgenologic studies. However, his progress at 19 months of age would make this possibility slight. The difference in prognosis suggests that the lesion in these patients is different.

Similar to the patients described by Butler et al.[12] but in an older age category are the patients reported by Rule and Grollman,[13] Boyd and Stearns,[14] Baines, Barclay and Cooke,[15] and Albright, Burnett, Parson, Reifenstein and Roos[6] and others. Albright's opinion that the osseous changes in these patients follow the chronic acidosis is a reasonable one. If such is the case, it is interesting to speculate as to whether the patient in Case 2 will develop abnormalities of calcium and phosphorus metabolism at a later date or if the therapy will prevent these complications. Since all but one of the patients with the hyperchloremic, low plasma bicarbonate pattern had renal calcifications when first seen, it would seem unlikely that Case 2 will develop them, and there is even less reason to suspect that Case 1 will have such trouble.

Probably the most complicated example of failure of tubular function is that of the DeToni-Fanconi syndrome which was so well described by McCune, Mason and Clarke.[16] In these the mechanism of the acidosis was different from that in our patients.

Summary

Two infants are described, both of whom had unexplained signs of anorexia, vomiting, dehydration, fever and acidosis. Both probably had defects in reabsorption of bicarbonate in the renal tubules without other evidence of anatomic renal disease.

The symptoms of both infants were relieved by the administration of alkaline salts. One patient, after a year of therapy, recovered and has developed normally without further treatment. The other still requires alkaline salts to prevent the development of acidosis.

Supplementary Note

Since this paper was submitted for publication a report of a similar case has come to the attention of the authors (Stapleton, T., Idiopathic renal acidosis in infant with excessive loss of bicarbonate in urine, Lancet 1:683, 1949). This was an infant with chronic vomiting, constipation and failure to gain weight who responded to the protracted administration of alkali by mouth.

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Spanish Abstract

Acidosis Crónica de Origen Renal en Infancia

Se describen dos infantes, ambos de los cuales tenían signos inexplicables de anorexia, vomitos, deshidratación, fiebre y acidosis. Ambos probablemente tenían defectos en resorción de bicarbonato en los túbulos renales sin otra prueba de enfermedad renal anatómica.

Los síntomas de ambos infantes fueron aliviados mediante la administración de sales alcalinas. Un paciente, después de un año de terapia, se restableció y se desarrolló normalmente sin más tratamiento. El otro todavía require sales alcalinas para evitar el desarrollo de acidosis.

Bowman Gray School of Medicine, Wake Forest College

CLINICAL STUDIES OF THE EFFECTS OF 3,5,5,-TRIMETHYLOXAZOLIDINE-2-4-DIONE (TRIDIONE®) ON THE HEMATOPOIETIC SYSTEM, LIVER AND KIDNEY

By ERIC DENHOFF, M.D., AND MAURICE W. LAUFER, M.D.,
with the technical assistance of Daniel V. Tramonti, B.S.
Riverside, R.I.

THE clinical worth of 3,5,5,-trimethyloxazolidine-2-4-dione (tridione®) has been proved in the treatment of the petit mal triad in epilepsy. However, reports have appeared of possible adverse effects upon the hematopoietic system.[1,2] These have led to the use of laboratory measures, such as repeated complete blood cell and platelet counts, in an attempt to avoid such occurrences. It is not yet certain, however, whether these represent the best available indicators of possible toxicity.

A study was accordingly performed on children with convulsive disorders who were resident patients at the Emma Pendleton Bradley Home, a neuropsychiatric hospital for children. Its purpose was to evaluate the possible toxic effects of tridione® and to seek simple laboratory procedures that could be utilized as early indicators of toxicity.

MATERIAL AND METHODS

Six children receiving tridione® in clinical dosage were studied over periods from 6 to 16 mo. Five of these subjects had petit mal epilepsy, while one had cerebral palsy and a grand mal convulsive disorder. The children also received various anticonvulsant medications at some time during the period of study.

Seven other patients were utilized as controls. Five of these received dextro- or levo-rotatory $C_6H_5CH_2CH(NH_2)CH_3$ (amphetamine®) during the period of study while 2 others received no medication whatsoever.

Tests were chosen to investigate the hematopoietic system as well as liver and kidney function. The methods utilized were all standard technics.[3] Blood studies included RBC count, photoelectric hemoglobin, WBC count, differential leukocyte count, hematocrit, sedimentation rate, reticulocyte count, bleeding-clotting time, fragility tests, platelet determinations[4] and clot retraction time.[5] These were performed usually at weekly intervals. Bone marrow studies were done at monthly intervals.

Liver function studies included: icterus index; total protein;[6] bromsulphthalein;[7] prothrombin time;[8] cephalin-cholesterol test;[9] blood bilirubin;[10] quantitative and qualitative stool and urine urobilinogen.[11] These were also performed weekly. Studies of renal function included: complete urinalysis; phenosulphthalein excretion time; porphyrin; blood urea nitrogen;[12] cholesterol.[13] These too were done at regularly scheduled periods.

All test procedures were carried out on the normal controls to determine standards of normality for this particular hospital population. Except for platelet determinations, all test results came within generally accepted standards. Using a modified Fonio's method,* the platelet values in the control group ranged from 119,600 to 408,800 platelets/cmm. with an average of 250,000/cmm.

From the Emma Pendleton Bradley Home, Riverside, R.I.

Supported in part by a grant from the Abbott Research Laboratories under the direction of Dr. R. K. Richards, for which acknowledgment is gratefully made.

(Received for publication Aug. 1, 1949.)

* Present methods of counting blood platelets are unsatisfactory, not only because of the differences in method and individual technic, but because there are many physiologic variations.[14] The most reliable platelet counts are obtained when one technician standardizes on one technic. Initially, Fonio's

Bone marrow aspirations were obtained in a standard manner.[17] Differential cell counts were reported as an average of 3 readings of 300 cells each. The normals approximated those reported in children.[17] Megakaryocyte counts were performed by drawing marrow blood with a white cell pipette up to the 0.5 mark and diluting to the 11 mark with a diluting fluid consisting of 2% gentian violet solution in white cell diluting fluid. The material was mixed well and placed in the white cell counting chamber. Several determinations were done from one pipette and the results averaged. As the normals vary with the laboratory,[18] in this study the value regarded as normal was 50 to 150 megakaryocytes/cmm.

Results

Red Blood Cells: There was no evidence of anemia in those patients receiving tridione®. The red blood cell counts consistently remained above 4.0 million/cmm., while the hemoglobin did not fall below 12 gm./100 cc. The reticulocyte count varied from 0.4% to 1.5%, while sedimentation rates were not elevated. Serum iron determinations, performed in a few cases, were also normal. In one patient (Case 3) slight anisocytosis and poikilocytosis began 18 weeks after therapy was started, and beginning endoglobular degeneration became evident after 31 weeks of tridione therapy.

Leukocytes: Granulocytopenia was not noted, although three children developed total white blood cell counts below 5.0 thousand/cmm. This also was noted after 23 to 38 weeks of therapy (Cases 1, 3, 5). When the drug was discontinued, the cell count reached normal within a week in two cases and within 10 weeks in the third (but this patient was receiving another medication in the interim).

In three cases (3, 4, 6) a markedly increased number of lobulated lymphocytes (30 to 40%) with clumped basophilic cytoplasm containing many vacuoles was noted beginning from the 9th to 13th week of tridione therapy. This finding was generally associated with a significant elevation of the eosinophile count.

Platelet Count: Three patients (Cases 1, 3, 6) developed low platelet counts ranging from 60,000 to 100,000/cmm. Two cases (1, 6) developed this early (three to seven weeks), while one case (3) developed this finding during the 22nd week of therapy. However, the platelet values became normal approximately one week after the cessation of the drug therapy.

Clot Retraction: The clot retraction time progressively increased to abnormal values (Case 1—33 weeks; Case 3—21 weeks; Case 6—9 weeks) in the same three patients. While the normals had an initial clot retraction at ½ hour, definite by 1 to 1½ hours, these patients showed initial retraction in 2 to 2½ hours, definite by 3 to 3½ hours.

Other measurements for bleeding abnormalities, such as bleeding-clotting time, prothrombin time, blood fragility and Rumpel-Leeds Test remained within normal limits.

Liver Function Studies: Cephalin-cholesterol tests for liver function in two cases were significantly changed (Cases 1, 3). It is interesting that the change occurred during periods when there was retardation of the clot retraction time. Other studies of liver function were within normal limits.

Kidney Function Tests: There was no laboratory evidence of impaired renal function. Urinalysis, phenolsulfonphthalein excretion time and blood urea nitrogen values remained

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method, which gives the lowest normal values[15] but is simple and reliable, was utilized. This was at first modified by using Na citrate.[4] Later the method was further modified by counting platelets directly from a stained blood smear, without utilizing any diluting medium. The results were strictly comparable to those obtained from simultaneous smears from the same patients made with the dilution technic. The stained smear technic is regarded as reliable by Dameshek.[16]

within normal limits. The blood cholesterol, utilized as a possible indicator of glomerular or tubular damage, never was elevated.

Bone Marrow Aspirations: These could be carried out in only five of the patients. The bone marrow differential count seemed significantly affected by tridione® in two of them (Cases 3, 4). After 3 weeks and 12 weeks of therapy, respectively, a decrease in nucleated red blood cells and megakaryocytes along with a slight increase in non-segmented polymorphonuclears was observed. The percentage of nucleated red cells dropped from 20% to 7-10%, and the megakaryocytes from approximately 30-100/cmm. to 2-5/cmm. The megakaryocyte and nonsegmented polymorphonuclear response seemed very labile in that after the discontinuance of tridione® values rose rapidly to normal. In two cases also the depressive response was only temporary, with a rise to normal even while the drug was continued. The nucleated red blood cells responded more slowly, but in a similar manner.

Special Study: Two patients (Case 6 and Case 7, a normal control) were observed during a 40 day period, during which time tridione® was administered on two separate occasions (Charts 6a and 7). Prior to the medication all hematologic values were within normal limits.

To both patients tridione® 0.3 gm. daily was administered for eight days. At the end of that period the clot retraction values and platelets were within normal limits. However, in both patients the percentage of nucleated red blood cells in the bone marrow showed a decline. In Case 6 this value dropped from 17.5% to 7% and in Case 7 from 13% to 10%. The megakaryocyte count fell similarly (Case 6, from 35/cmm. to 3/cmm.; Case 7, from 35/cmm. to 7/cmm.).

The drug was then discontinued for five days. By that time, although there was no significant change in the peripheral blood, the bone marrow showed a compensatory rise in nucleated red blood cells and megakaryocytes. The figures for Case 6 showed a rise in red blood cells from 7 to 20% and in megakaryocytes from 3 to 100/cmm. The corresponding rise in Case 7 was from 10% to 15% red blood cells and in megakaryocytes from 15 to 43/cmm.

Following this five day free interval, tridione® was again administered in a larger dose, 0.6 gm. every 24 hours, for a period of 15 days and the blood studied at weekly intervals during this time. There were no significant changes in the peripheral blood. Although the bone marrow findings were within normal limits at the onset of the period, at its conclusion the following changes were noted: in Case 6 the nucleated red blood cells fell from 20% to 12.5% and the megakaryocytes from 100 to 30/cmm. In Case 7 the nonsegmented polymorphonuclear cells increased from 29% to 40%, while the nucleated red blood cells fell from 15% to 11.5%, and the megakaryocytes from 43 to 5/cmm.

The tridione® was then reduced in dosage to 0.3 gm., which was given daily for four more days. At the end of this period the reduction in nucleated red blood cells and megakaryocytes was even more marked. In Case 6 the nucleated red blood cells decreased from 12.5% to 3.5%, and the megakaryocytes from 30 to 1/cmm. In Case 7 the nucleated red blood cells fell from 11.5% to 3%, and the megakaryocytes from 5 to 2/cmm.

The drug was then discontinued and laboratory procedures repeated in seven days. Again, there was a sharp rise. In Case 6 the red blood cells increased from 3.5% to 20%

and the megakaryocytes from 1 to 50/cmm., while in Case 7 the nucleated red blood cells rose from 3.5% to 14% and the megakaryocytes from 2 to 23/cmm.

Case Studies

Case 1. This 10 yr. old boy was admitted because of a convulsive disorder manifested by grand and petit mal (Chart 1). Tridione® 0.9 gm./day was administered. During the next 3 mo. the dose was gradually increased to 1.2 gm. daily. Although the platelet counts during this initial 3 mo. period averaged 300,000/cmm., the 67th day after treatment was begun, there was a sharp drop in the platelet level to 50,000/cmm.

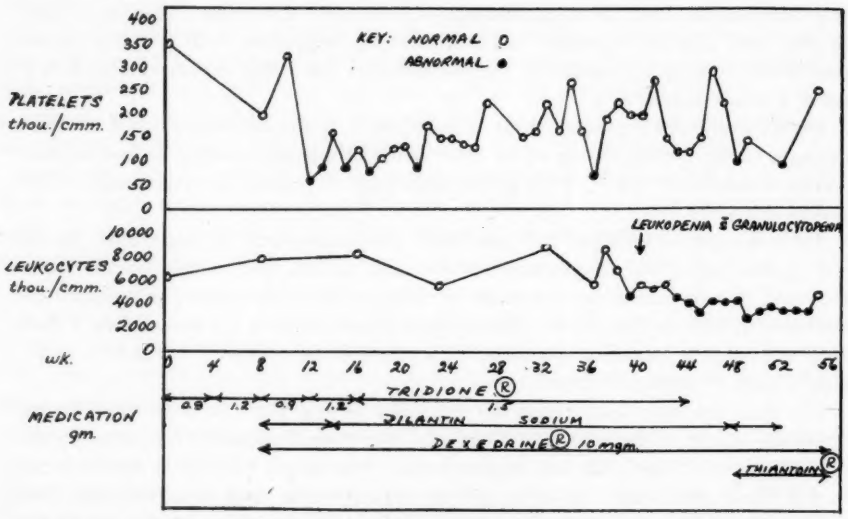

Chart 1. 10 yr. old boy developed drop in platelets 3 wk. after start of tridione®. Fluctuations in abnormal platelet levels persisted for 25 wk. Treatment was continued. Ten months after tridione® was first given, leukopenia without granulocytopenia and prolonged clot retraction time was noted. Drug was discontinued without after effects.

During the next 6 wk., platelet values fluctuated between low normal and abnormally low values. There were no other significant changes, nor were there any clinical signs of bleeding.

The dosage of tridione® was increased to 1.5 gm. daily, in spite of low platelet counts, because of the need to control seizures. Shortly after, the platelet count rose and maintained normal values for 7 mo. when a single low value was recorded. Nine months after tridione therapy was first initiated, leukopenia without granulocytopenia (white blood cells 4.0 thousand/cmm. with 40% polymorphonuclears) was first noted.

One week and 2 wk. later a slight prolongation in clot retraction time was noted (slight initial retraction, 2 hr.; complete retraction, 3 hr.; definite retraction, 24 hr.). A similar finding was recorded the next week. Rumpel-Leeds Tests for petechial hemorrhages were performed but were negative. Cephalin flocculation tests, which had previously been normal, now showed a 2+ reaction.

Tridione® was discontinued after a total of 10 mo. Clot retraction time then returned to normal within 1 wk. as did the cephalin flocculation test within 8 wk. WBC count remained low for the next 10 wk., but then rose to within normal limits. It should be noted that during this period the patient was receiving another medication.

Discussion: In spite of low platelet values, tridione® was continued in this patient until leukopenia and the prolongation of the clot retraction time indicated definite toxic effects.

Case 2. This 10 yr. old boy was admitted because of grand mal and associated behavior disorder

(Chart 2). He received dilantin sodium and tridione® 0.9 gm. for a period of 3 mo. During this period all laboratory studies remained within normal limits. These studies were continued for the next 7 mo. to determine whether there were any after-effects following tridione therapy, and none were observed.

Case 3. This 8 yr. old girl with a spastic diplegia resulting from a birth injury was admitted for the treatment of convulsive disorder, grand mal (Chart 3). In order to evaluate the effect of tridione®

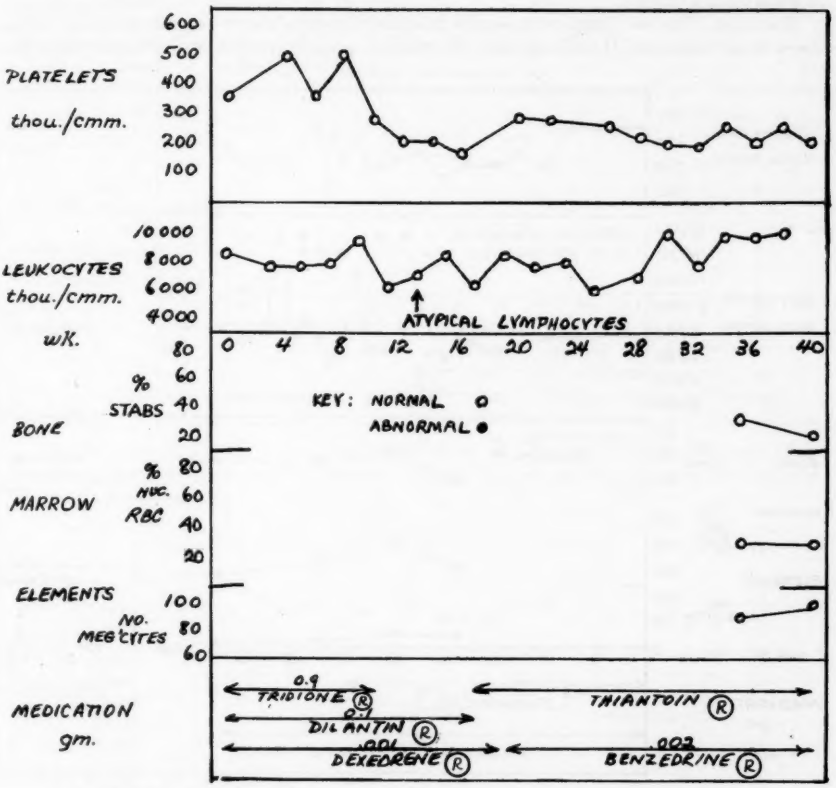

CHART 2. 10 yr. old boy who received tridione® without any deleterious effect to hematopoietic system.

on spastic states, she was given tridione® 0.3 gm. daily for a period of 45 days without any apparent toxic manifestations. The dosage of the drug was then increased to 0.6 gm. daily.

During the next 30 days the platelet count tended to decline toward the lower limits of normal. The bone marrow at this time revealed a low megakaryocyte count (7/cmm.). Although the RBC count and hemoglobin had been in the high normal range at the onset of the study, during this period the RBC counts averaged 4.2 million/cmm. and the hemoglobin 80%. The stained smears consistently showed achromia and slight macrocytosis. Although there was no leukopenia, at least 32% atypical lymphocytes (vacuolated and lobulated) were consistently observed. Repeated bone marrow aspirations during the next 2 mo. revealed the megakaryocytes were still depressed (between 1 and 7/cmm.), and there was a slight lowering of the nucleated red blood cell value (6 to 10/cmm.). Simultaneously the cephalin flocculation tests, which had been normal, showed first a 1+ and then a 3+ reaction.

During the 7th week of tridione treatment the platelet count fluctuated erratically, and the clot retraction time became slightly increased over normal values (initial, 2 hr.; definite, 3 hr.; complete,

24 hr.). The bone marrow at this time revealed a significant drop in megakaryocyte and nucleated red blood cell values.

Tridione® was then discontinued. The platelet count suddenly became elevated within 24 hr. and then gradually receded to midnormal values by 1 wk. The clot retraction time gradually became normal within 5 wk. Bone marrow findings remained unchanged for the next 2 mo. However, a follow-up study 9 mo. later revealed bone marrow essentially within normal limits except for a slight reduction in normoblasts (12.5%).

Discussion: This case illustrates a possible basic mechanism for the development of aplastic anemia due to drug intoxication. If the drug had been continued, a true irreversible aplastic picture might have

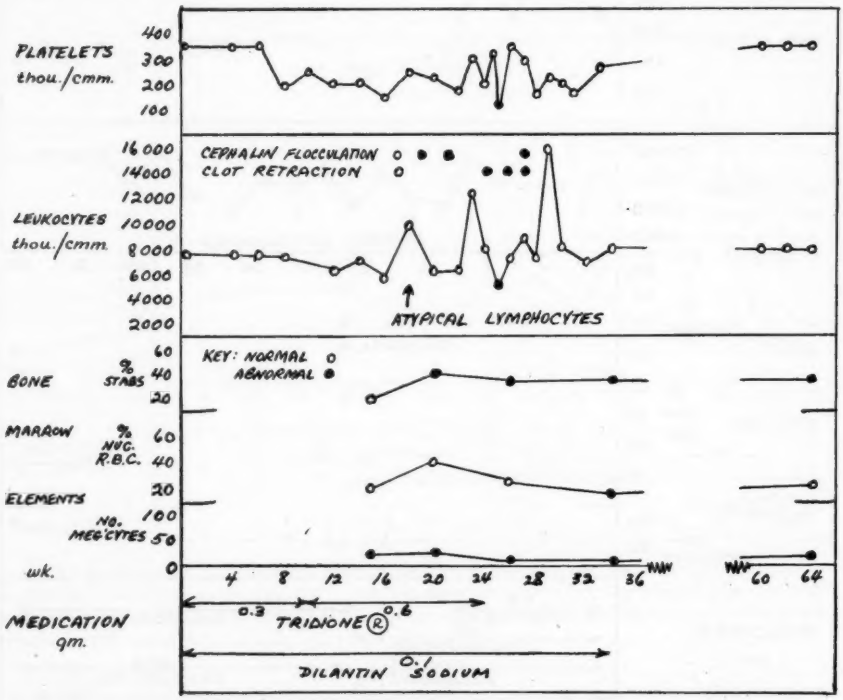

CHART 3. 8 yr. old girl received tridione® 0.3 gm. for 13 wk. without any toxic manifestations. When dose was increased to 0.6 gm., there was gradual drop in platelets and megakaryocytes. When drug was discontinued, peripheral blood values became normal. Bone marrow elements remained low for several weeks.

ensued. The findings in this case of combined low platelet counts, abnormal clot retraction, and abnormal bone marrow suggested the point at which tridione® should be discontinued. The follow-up study 9 mo. later emphasizes the temporary effect of tridione® on the blood elements.

Case 4. This 11¼ yr. old boy was admitted because of convulsive disorder, both grand and petit mal (Chart 4). During the 1st 4 mo. of hospitalization he had received thiantoin® and then dilantin sodium®. Laboratory studies, including several bone marrow aspirations, were essentially normal during this period.

Tridione® 0.3 gm. daily was begun. Twenty days later a bone marrow aspiration revealed a decrease in the nucleated RBC count to 12.5%, whereas the month previously it had been 20%. Similarly, the megakaryocyte count dropped sharply from 38/cmm. to zero. The nonsegmented polymorphonuclear leukocytes rose from normal limits to 40%. The findings in the peripheral blood were not remarkable.

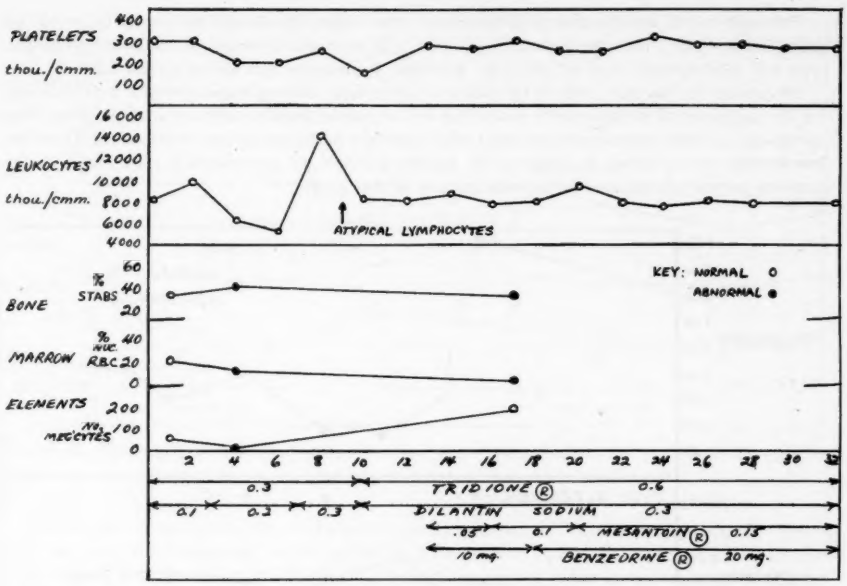

CHART 4. 11 yr. old boy received tridione® for 44 wk. There was no apparent toxic effect on peripheral blood, but bone marrow elements involved in tridione® reaction were affected early in course of administration.

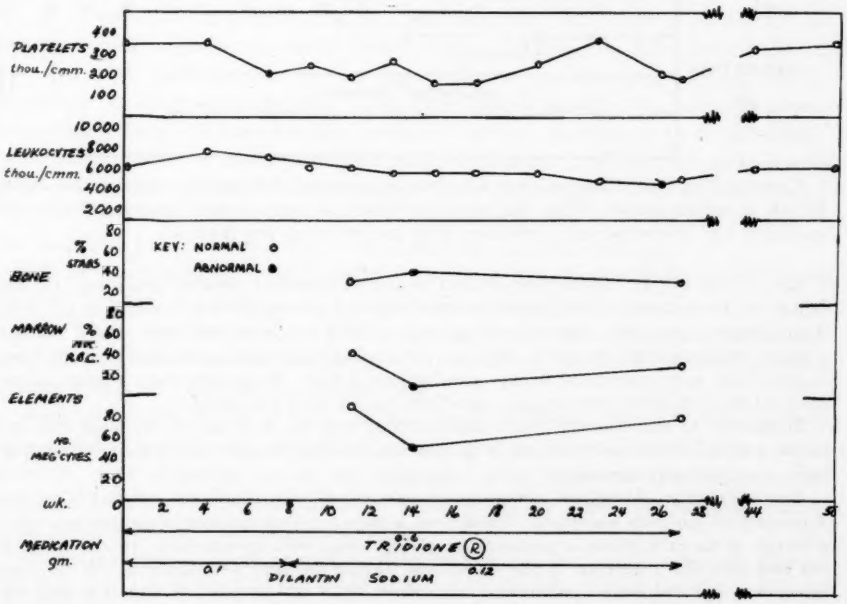

CHART 5. 8 yr. old boy received tridione® for 27 wk. without any abnormalities being noted. There was equivocal effect on bone marrow elements during 14th wk. of study.

Two and a half months after tridione therapy was begun, the dosage was increased to 0.6 gm. daily. Forty-two days later the nucleated red blood cells were still depressed, although the megakaryocytes had spontaneously risen to 100/cmm. All other studies remained within normal limits.

Discussion: In this case, early in the course of the tridione therapy megakaryocytes were decreased, but the inhibition of megakaryocyte production was overcome despite continuation of the drug. There seemed to be a more permanent depressant effect upon the nucleated red blood cell values. There was, however, no anemia shown in studies of the peripheral blood. No explanation is apparent for the rise in young polymorphonuclears in the bone marrow of this patient.

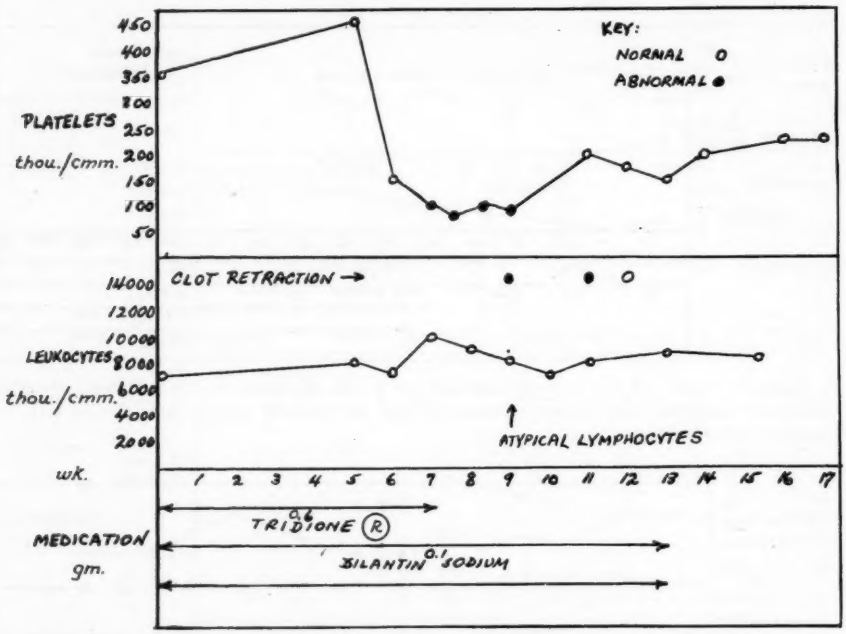

CHART 6. This 9 yr. old boy developed low platelet count and abnormal clot retraction time during 8th wk. of tridione therapy. When drug was discontinued, all values returned to normal. Patient was studied for 1 yr. after cessation of medication. Bone marrow studies were not done.

Case 5. This 8½ yr. old boy was admitted because of convulsive disorder, grand and petit mal (Chart 5). He was immediately placed upon tridione® 0.6 gm. and dilantin sodium 0.12 gm. daily. Approximately 4 mo. later a bone marrow aspiration revealed a nucleated RBC count of 6%, although a month previously it had been 29%. Similarly, the megakaryocyte count had dropped from 150/cmm. to zero. There were no abnormal findings in the peripheral blood. Three months later, despite continuation of tridione®, in the same dosage, a repeat bone marrow study was normal.

Discussion: In this case there was a single occasion with low bone marrow red blood cells and megakaryocytes unassociated with any peripheral abnormalities. Despite continuation of the drug, these values returned to normal.

Case 6. This 9 yr. old boy was admitted for a convulsive disorder, grand and petit mal (Chart 6). Tridione® 0.6 gm. daily was started. Within 6 wk. a sharp and consistent drop in platelets was noted. Although in the early phases of treatment the platelet values were approximately 430,000/cmm., at this time they fell to between 50,000-90,000/cmm. During the same week abnormal clot retraction values were recorded (initial retraction, 2 hr.; definite, 2½-3 hr.; complete, 24 hr.). The drug was then discontinued, and in the following week both values became normal. Bone marrow aspirations were not done in this case.

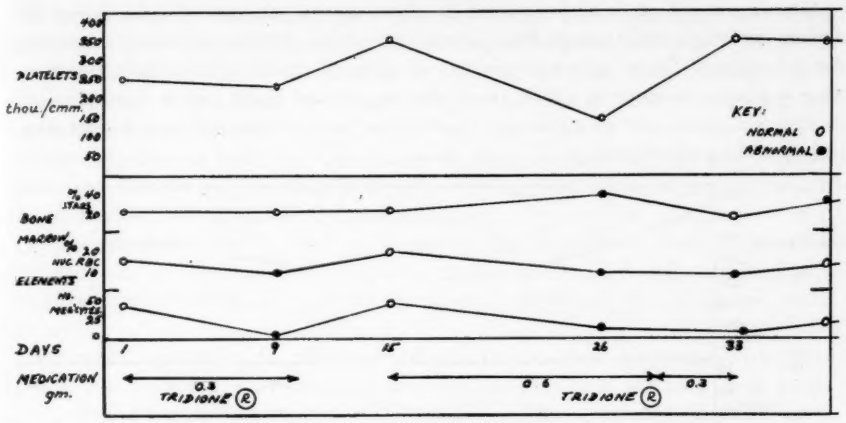

CHART 6a. Tridione® given on 2 occasions over 40 day period to patient previously showing no sensitivity reveals extreme sensitivity of bone marrow elements.

The patient was studied closely for the next 12 mo. to determine if there were any toxic after-effects from the drug. All hematologic values, including bone marrow aspirations, remained within normal limits. It was then decided to re-administer tridione® for a short period in order to determine if the results could be duplicated. These findings are reported under "Special Study" and Chart 6a.

DISCUSSION

Experience has shown that tridione® is a relatively safe drug when used judiciously. It can, however, cause granulocytopenia, and there have been reports of death from aplastic anemia following its use.[1,2] Results of the current study differ from others in that aberrations in blood elements have been found in some instances relatively early in the course of drug administration. These abnormalities occurred in a definite pattern and possibly form the basis for early evaluation of toxic reactions in these individuals.

In some patients at least, some bone marrow elements seem sensitive to tridione® even after a short period of administration. The megakaryocytes were the first affected, becoming depressed relatively readily. This depression in some cases was only temporary, however, with a rise to normal values even though the drug was continued.

Almost simultaneously the percentage of nucleated red blood cells diminished, while in some instances the nonsegmented polymorphonuclears became elevated. These values on the whole tended to rise and fall in accordance with the amount and duration of drug therapy, but without seeming to have any permanent effect upon the hematopoietic system. This is best illustrated by Charts 6a and 7.

After a variable period of time, in some cases the blood platelet values gradually diminished in number even though still remaining within accepted normal limits. Some, however, were definitely low by any standards. Later there was an increase in the initial and definite clot retraction times, although at the same time bleeding-clotting time, prothrombin time, etc., remained normal.

When the platelets were abnormally low and/or the clot retraction time increased, the drug was discontinued in this study. It would have been interesting to have continued medication in order to determine if these phenomena would affect the patient clinically. but in view of the possibilities of permanent damage, this was not done.

Anemia was not observed in spite of the depression of marrow red cells during the periods of drug administration. The patients showed no evidence of blood destruction due to tridione®. Some confirmation of this was given by studies of serum iron. However, there was some evidence of a toxic factor affecting the red blood cells in that variations in size and shape and endoglobular degeneration were occasionally noted after long periods of drug administration.

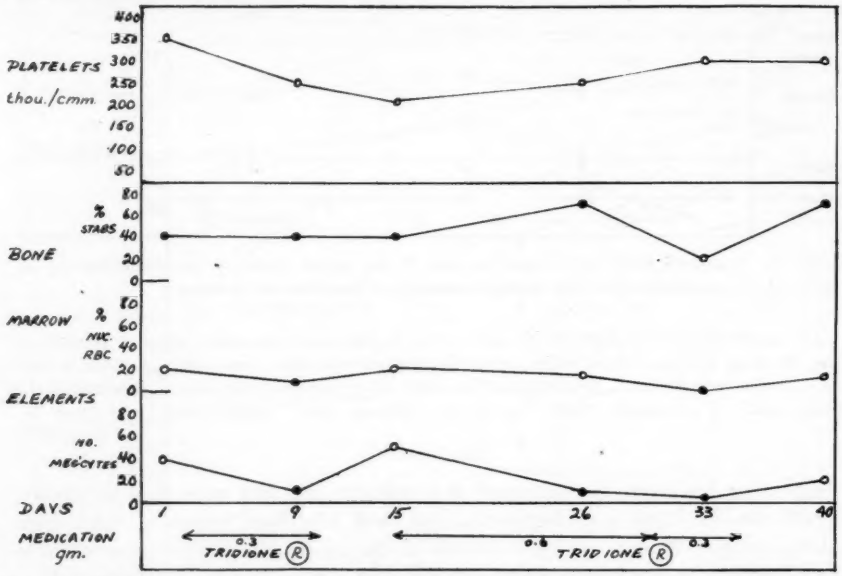

CHART 7. Tridione® was given to patiént who had never before received drug. Extreme sensitivity of bone marrow elements are demonstrated.

In these patients the drug did not seem to affect significantly the number of leukocytes except in a very few instances, and granulocytopenia was never observed. Nevertheless, a characteristic "atypical lymphocyte" in significant numbers was observed in four out of the six cases studied.

It has been suggested that sensitivity to the drug may be explained on the basis of allergy.[19] While the majority of our patients did develop a significant degree of eosinophilia, unfortunately all of them had pinworm infestation, a disease in which eosinophilia is common. In addition there was no clinical evidence of allergic phenomena, such as drug rash or urticaria. Skin patch tests with tridione® were negative in three of the patients. It is difficult, therefore, from this study to implicate any allergic factor.

The effect of tridione® on the hematopoietic system as observed during the 40 day special study period is worthy of discussion. The results indicated that the bone marrow could readily be altered even when the peripheral blood maintained its normal values. Charts 6a and 7 demonstrate the relative sensitivity of the bone marrow elements concerned in the tridione reaction and the lack of concurrent significant findings in the peripheral blood. From these reactions it would seem that tridione® may be a specific marrow depressor, since it affected the marrow of so many patients in a rather characteristic fashion.

In those patients who presented significant alterations of blood values, several changes tended to occur together. There was at first a depression of megakaryocytes which resulted in the diminution of the number of platelets, and was finally associated with delayed clot retraction. Along with these changes there was a decline in the nucleated red blood cells in the marrow.

Frequently, but not invariably, associated with these findings was a peripheral leukopenia, toxic signs in the red blood cells and in the lymphocytes. Occasionally there was a simultaneous rise in cephalin flocculation values.

The question immediately arises as to whether the sequence of blood changes just described may represent an early stage of a process which could eventually lead to a full-blown aplastic anemia. It is not possible to give a definite answer to this, for several reasons.

Because of possibilities of permanent damage, the drug was not continued in these patients past the point which has been described and this, if it had been done, would have provided the only conclusive evidence. There are also a number of points which suggest that—even if such a process does lead in some patients to aplastic anemia—it does not invariably do so. It was noted in some of the cases that there was a spontaneous reversal toward normalcy in the blood picture even while the drug was continued. In addition, since the incidence of aplastic anemia is so low (less than 1:10,000) it seems likely that there may be some idiosyncratic factor operating in those individuals who do develop the clinical picture of aplastic anemia.

If an individual has some idiosyncrasy which makes him particularly susceptible to tridione®, the described pattern of blood changes might represent the initial stage of a developing aplastic anemia. Until this point can be clearly elucidated, it would therefore seem wise to look for such blood picture changes in individuals receiving tridione®. If there is no spontaneous reversal of the pattern, withdrawal of the medication may be indicated.

The lack of information obtained from peripheral blood counts in contradistinction to the sensitivity of the bone marrow cells to tridione® tends to bear out Young's[20] recent conclusions that leukocyte counts during the administration of agranulocytosis producing drugs are of no value in the prophylaxis of that condition, since agranulocytosis may be fully established in the bone marrow before the peripheral blood gives any warning. Young discusses the bone marrow mechanism in agranulocytosis based on the reports of several other workers. In agranulocytosis, the myeloid bone marrow has been found to be aplastic, normal or hyperplastic, and there is evidence to suggest that when the specific agranulocytosis producing drug is discontinued, recovery occurs only in those marrows which show an increase of granulocytes. This impression is based on Rosenthal's and Vogel's[21] studies of three cases of agranulocytosis resulting from sulfapyridine. Although there was a diminution in the total marrow cell count in all three patients, the myelocytes were markedly increased in the one that recovered while death ensued in two others with a relative increase in lymphocytes and normoblasts. Perhaps not only do such cases have a good prognosis for recovery, but it even may be that with such a bone marrow picture, treatment can be cautiously continued.

The exact pattern reported in those cases has not been found with tridione®, although there were certain similarities and it is possible that the entire picture might have been reproduced had the drug been continued.

There was a tendency for the nonsegmented polymorphonuclear cells to be increased

at irregular intervals during periods of increased or prolonged drug administration. This mechanism was more outstanding in Case 4 of the clinical series and in Case 7 of the special study. This increase in granulocytes may imply that tridione®, like so many other drugs, may depress the production and delivery of mature granulocytes, manifested in the marrow as a stimulation of the younger granulocytes with the failure to progress beyond this stage.

From the practical point of view, in the hands of the average practitioner or laboratory, the clot retraction time seems the simplest and most reliable technic to use as a single indicator, particularly when it is combined with complete blood cell counts. The danger point seems to be delay in clot retraction to: initial retraction, two hours or more; definite retraction, three hours or more. Bone marrow studies are of obvious value but less readily available. A depression of megakaryocytes may be of particular significance in suggesting possible tridione sensitivity early. If the megakaryocyte level spontaneously returns to normal even while the patient remains on medication, then it is probably safe to continue with the tridione®. A persistence of the low megakaryocyte values must, however, be regarded as a danger signal.

Conclusions

Six children receiving tridione® showed: 1. A constant syndrome of: a decline in bone marrow megakaryocyte and nucleated red blood cell elements; a low peripheral blood platelet count; and prolonged clot retraction time. 2. An occasional association of: peripheral leukopenia, toxic signs in the red blood cells and lymphocytes, and an abnormal cephalin flocculation response.

In one case the bone marrow megakaryocyte response occurred alone and was temporary; in another it was temporary but associated with a persistent decline in marrow nucleated red blood cells; and in a third case both the megakaryocyte and nucleated red blood cell depression were only temporary, despite continuation of the medication.

Withdrawal of medication caused a return to normal values, most rapid and marked in the bone marrow.

Tests for clot retraction time and platelet counts at regular intervals in addition to complete blood counts seem indicated in all patients receiving tridione®. When available, bone marrow studies, especially of megakaryocytes, would also be of value.

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SPANISH ABSTRACT

Estudios Clinicos de los Efectos de Trimetiloxazolidina-3,5,5, Dione-2-4 (Tridiona®) sobre el Sistema Hematopoyético, Hígado y Riñón

Seis niños que recibieron tridiona® en dosis clínica fueron estudiados por períodos de 6 a 16 meses, con análisis de la sangre periferal y de la médula del hueso. Hubo un síndroma constante de: una decadencia en megacariocitos de médula de hueso y elementos de glóbulos rojos nucleados; un cuento de plaquete de sangre periferal bajo; y tiempo de retracción de coágulo prolongado. Hubo una asociación ocasional de: Leucopenia periferal, señnas tóxicas en los glóbulos rojos y linfocitos, y una respuesta de floculación cefalina anormal. La retirada de la medicación causó un regreso a los valores normales, el más rápido y marcado fué en la médula del hueso.

Es posible que pudiera haber habido una respuesta aplástica en algunos de estos pacientes si la droga se hubiera continuado en alta dosis. Como la leucopenia periferal fué solamente un descubrimiento ocasional, la dependencia sobre este análisis solo puede indicar que tal proceso estaba pasando. En este estudio, la técnica más simple y en la cual se puede depender más para usarla como un simple indicador pareció ser el tiempo de retracción de coágulo. Se creyó que el punto peligroso hubiese sido un retardo en retracción de coágulo a: retracción inicial, 2 horas o más; retracción final, 3 horas o más. Los estudios de médula de hueso, aunque menos disponibles, fueron también de bastante valor. Una depresión de megacariocitos pudo ser de particular significancia sugiriendo posible sensibilidad tridiona® temprano. Si la cantidad de megacariocitos regresó espontaneamente a normal, aún mientras el paciente quedara en tratamiento, era probablemente seguro continuar con la tridiona®. Una persistencia de un valor de megacariocitos bajo fué, sin embargo, mirado como un signo de peligro.

Emma Pendleton Bradley Home

CARDIAC AND AORTIC ARCH ANOMALIES IN THE OFFSPRING OF VITAMIN A DEFICIENT RATS CORRELATED WITH SIMILAR HUMAN ANOMALIES

By JAMES G. WILSON, M.D., AND JOSEF WARKANY, M.D.
Cincinnati

INTEREST in congenital malformations of the heart has increased in recent years. Roentgenologic, electrocardiographic and other clinical methods now make possible the diagnosis of many types of congenital cardiac malformations which previously could not be recognized during life. Progress in diagnostic and operative technic has led to excellent results in cardiac surgery and a better prognosis for many children with congenital heart disease. Simultaneously, there has arisen a renewed interest in the etiology and development of congenital malformations of the heart.

Regarding etiology, many students of this subject (Abbott,[1] Brown,[2] Thomson,[3] Schoenberg[4] and others) have concluded that genetic factors are not prominent in the causation of congenital cardiac anomalies, although in rare instances certain defects have been attributed to inheritance. Septal defects in a parent and child were observed by Debré,[5] Seitz and Baumann[6] (father and four children), Walker and Ellis[7] and Tucker and Kinney.[8] Patent ductus arteriosus was reported in a father and four of his children by Walker and Ellis[7] and in a man, two of his children and two grandchildren by Taussig.[9] Coarctation of the aorta in father and son was described by Walker.[10] Brown[2] states that dextrocardia in four generations of one family was described by Lancisi in 1701 and in three generations by Muir. It has been frequently reported that there is a high incidence of congenital heart disease in arachnodactyly[2,9] which is often inherited as a dominant trait. These examples suggest that occasionally congenital anomalies of the heart are inherited by a dominant mode of transmission.

When congenital anomalies of the heart are observed in more than one member of a family, they are more often seen in siblings than in successive generations.[1] This fact can be interpreted in two ways: either as a manifestation of recessive inheritance or as the result of unfavorable environmental (including maternal) conditions common to several pregnancies. That recessive inheritance may play a role in the causation of congenital heart disease in indicated by several observations. Roesler,[11] as well as Lamy and Schweisguth,[12] found a higher incidence of consanguinity among the parents of children with congenital heart disease than in the general population. Congenital heart disease sometimes occurs in syndromes which are considered genetic in origin and

From the Department of Anatomy, School of Medicine and Dentistry, University of Rochester, N.Y., and from the Children's Hospital Research Foundation, Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

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inherited as recessive traits. Cockayne[13] has pointed out that there is, in addition to dextrocardia, a high incidence of congenital heart disease in individuals with complete transposition of the viscera, an anomaly which he considers to be inherited as a recessive trait. Similarly, anomalies of the heart are not rare in patients with gargoylism or with the Laurence-Moon-Biedl syndrome, which are both thought to be inherited as recessive traits. Thus it is likely that in certain instances congenital anomalies of the heart are genetically determined.

On the other hand, there is no doubt that the heart can be deformed by adverse environmental conditions in early fetal life. This has been demonstrated clearly by the finding of congenital cardiac defects, such as patent ductus arteriosus, patent foramen ovale and interventricular septal defect in children whose mothers had rubella in the first two months of pregnancy.[14, 15] Other maternal factors are probably responsible for congenital anomalies of the heart which occur in mongoloid children. The nature of these factors is not yet known but they are present in older mothers more often than in younger ones.

It may be said, then, that genetic as well as environmental factors may determine abnormal development of the heart. However, in the majority of children with congenital heart disease, the determining etiologic factor remains obscure.

It is of interest that in rat experiments disturbance of the embryo brought about by maternal dietary deficiency may result in congenital malformations of the heart and the great vessels. Such experiments do not simulate human conditions and it is not suggested that dietary deficiency of the mother is an important cause of congenital cardiac malformations in man. However, it should be kept in mind that nutritional disturbance of the fetus may be induced by factors other than maternal dietary deficiency. Maternal disease, maternal metabolic imbalance, or anomalies of the embryonic membranes or placenta have been proposed as conditions which may interrupt the normal nutrition of the embryo and thus may conceivably result in anomalous development. In this sense, the experiments presented here could exemplify a mechanism by which malformations may be brought about through interference with the normal metabolism of the embryo.

The offspring of female rats fed vitamin A deficient diets prior to and during pregnancy are known to bear congenital malformations in several organ-systems.[16] Approximately 75% of such offspring had various developmental anomalies of the eyes.[17] Numerous malformations were found in the genito-urinary organs,[18] and some of these were almost as frequent in occurrence as the ocular defects. Anomalies of the heart and major thoracic arteries were noted less frequently, but these are of particular interest because they show remarkable similarity to many congenital cardiovascular conditions that occur in man. An embryologic and anatomic analysis of these defects in the heart and major arteries of the rat has recently been presented.[19] The purpose of the present report is to emphasize the similarities between the cardiovascular anomalies produced experimentally in the rat and some of those which occur "spontaneously" in man. Thereby, it is hoped that analogies drawn between the anomalies in the two species may contribute toward a better understanding of these conditions in human beings.

Methods

The method by which vitamin A deficiency was induced and maintained in female rats has been described in detail elsewhere,[17] and only a summary of the general experimental procedures need be presented here. After weaning, young female rats were placed on a diet that was nutritionally ade-

quate but contained only the minimal quantity of carotene that would permit continued growth. Presumably this allowed for little or no storage of vitamin A. This diet was continued until the animals reached a weight of 160 gm. at which time they were approximately 3 mo. of age and had attained sexual maturity. The females were then given a purified diet containing no carotene or vitamin A, and were given the opportunity to breed with males of the same strain that had been fed an adequate diet. Successful matings were indicated by the presence of sperm in the vaginal smear. The incidence and course of pregnancy was determined by taking daily weight and vaginal smear records. Of a group of 400 females subjected to this procedure, 334 mated, as evidenced by sperm in the vaginal smear; but no offspring were obtained from 184 of these due to early resorption or other forms of gestational failure. Offspring were obtained from 150 females, but only 37 of the mothers carried their young to term on the 22nd day. Fetuses were removed from 113 females between the 13th and 21st days, when it became apparent that pregnancy might be terminated spontaneously. Thus a total of 1,168 young was obtained.

As mentioned, about 75% of the offspring from vitamin A deficient mothers possessed some developmental defect of the eyes. No instance has yet been found of another anomaly existing in the absence of ocular malformation. Therefore, using ocular abnormality as a criterion, 64 fetuses and newborns known to be affected by maternal vitamin A deficiency were selected for study of the heart and major thoracic arteries. Only fetuses of 17 days' gestational age and older were included in this group since the definitive conditions of the cardiac septa and of the aortic arches are not normally attained until shortly before the 17th day. The animals thus selected from the young of vitamin A deficient mothers, together with 19 control fetuses and newborns of comparable age from mothers fed an adequate diet, were serially sectioned and prepared for microscopic study. Wax-plate reconstructions of the heart and major arteries were prepared from 5 animals in which these viscera were malformed, and from 2 of the controls, in order to verify the accuracy with which anomalies could be diagnosed from a study of serial sections. Many of the young sectioned were selected because of their abnormal appearance or because of conspicuous anomalies of the eyes. The percentage incidence of cardiovascular malformations in this selected group of fetuses is, therefore, probably higher than that in the total of offspring obtained from all pregnancies in this experiment.

Results

Septal Defects

Interventricular Septal Defect: Normally the interventricular septum is completely closed in the rat by the 17th day of gestation.[19] However, in 22 of 64 fetuses and newborns (34.4%) removed from vitamin A deficient mothers between the 17th and 22nd days of gestation, the septum was not closed and a foramen of variable size persisted between the right and left ventricles. In a majority of these the defect was localized in the base of the septum (Fig. 1). The defects in three fetuses were of such small size that it is doubtful they would have been of any functional significance in postnatal life. On the other hand, five fetuses possessed interventricular foramina of sufficiently large size to indicate that the muscular as well as the membranous septum was deficient. In three of these, the interventricular defect was associated with incomplete closure of the caudal end of the aortic-pulmonary septum. The heart in one of the latter resembled the condition Cor triloculare biatrium in that the ventricular region consisted of a single chamber, with only slight indication of even the muscular septum. In several instances the origin of the aorta appeared to be dextraposed and to override the septal defect, simulating the Eisenmenger complex of human cardiology. Since the position of the aorta may change in early postnatal life, and undergo a relative shift to the left, thus correcting the dextroposition, the final outcome might still have been a simple interventricular defect.

It is evident from the foregoing that the interventricular septal defects observed in rats

were morphologically similar to and covered about the same range of variation as the comparable defect in man. In both species this anomaly has been found more often in association with other cardiovascular defects than as an isolated anomaly. Only 6 of 22 cases in rats occurred in the absence of any other cardiovascular malformation. Abbott[20] cites 274 instances in man, of which only 50 were not complicated by other defects of the heart or major arteries.

The present authors know of no attempt to correlate the occurrence of interventricular defect with that of any particular aortic arch anomalies in man, although such a correlation has been possible to some extent in the animals used in this study. It was noted[19] that the

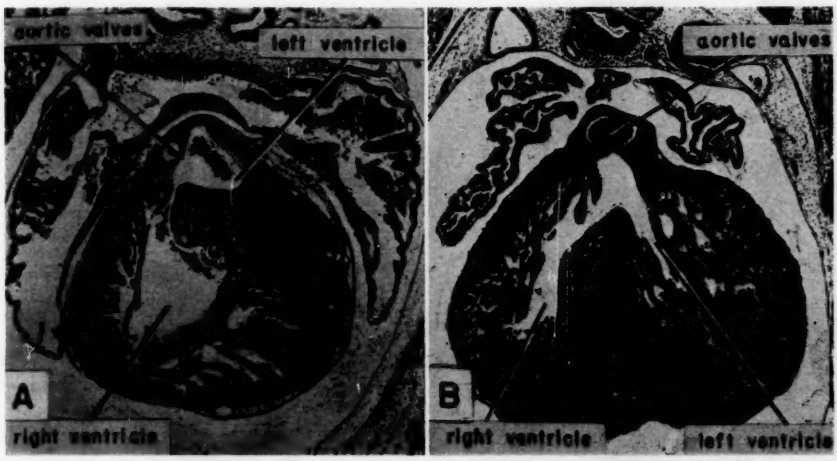

FIG. 1. Sections of hearts of abnormal young rats from vitamin A deficient mothers. A. Small interventricular defect. B. Larger interventricular defect.

septum always remained open when the arch of the aorta (fourth embryonic arch) was absent, or when a ductus arteriosus (sixth embryonic arch) failed to form or to remain patent during the latter part of fetal life. In either circumstance the ventricles of the heart could not have developed properly unless the interventricular septum had remained open to provide a shunt from one chamber to the other (except in the rare contingency of a persisting third embryonic arch). Conversely, the septum was rarely open when the persisting embryonic arches connecting the heart with the descending aorta exceeded the usual number. If similar correlations could be established for human cardiovascular anomalies, such information might prove useful in clinical or surgical considerations.

Aortico-Pulmonary Septal Defect: In addition to the three cases mentioned in which the caudal end of the aortico-pulmonary septum was incomplete, there was found in one specimen a more extensive defect of this septum. In this case, which is described on page 718 in detail, there was a partial truncus communis persistens. The ascending aorta and the pulmonary trunk were confluent in their proximal and distal portions, being separated only in a short middle segment. Partial truncus arteriosus communis was described as early as 1875 by von Rokitansky and by Clarke in 1885.[21] In an analysis of 1000 cases of congenital cardiac disease, Abbott[20] reported 10 cases of partial and 21 of complete truncus persistens.

Aortic Arch Anomalies

As employed here, the term "aortic arch anomaly" refers to any divergence from the normal pattern in the major arteries that are derived from the aortic arch system of the embryo. Aortic arch anomalies were found in 22 of the 64 fetuses and newborns from vitamin A deficient mothers. This rate of incidence happens to be the same as that noted for interventricular septal defect, but as already stated these two types of cardiovascular malformation did not always occur simultaneously. In 16 instances aortic arch anomalies were associated with open ventricular septum, but in six cases they occurred alone.

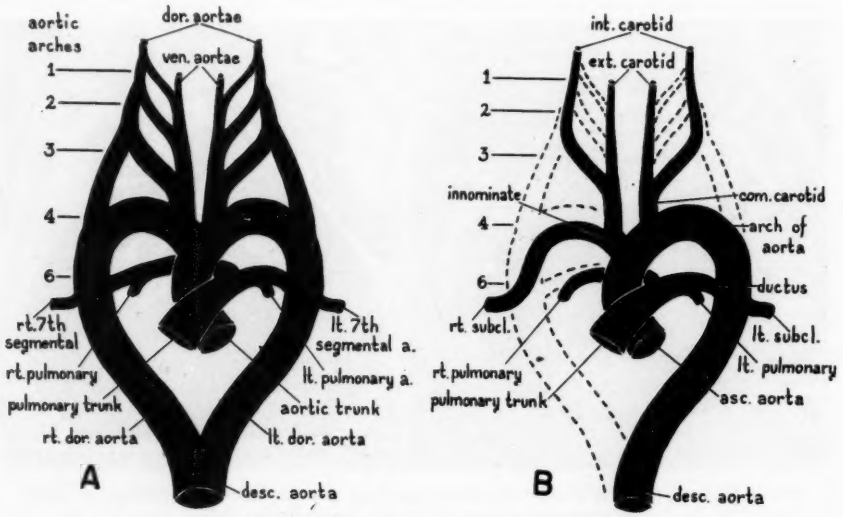

FIG. 2. A. Hypothetic embryonic pattern of aortic arches. At no time during development in mammals are all arches present simultaneously, but they are represented here in cumulative arrangement in order to emphasize their positional relationships. B. Definitive pattern of arteries derived from embryonic aortic arch system. Parts of embryonic system that underwent complete or partial regression are indicated in broken lines.

The aortic arch system of the embryo is transformed into the definitive pattern of major arteries of the chest and neck by processes involving retention of some embryonic parts and involution of others. These processes of differentiation are normally completed by the 16th day of gestation in the rat.[19]

A total of six pairs of aortic arches is said to comprise the aortic arch system of higher vertebrates; but in most mammals, including rat and man, the fifth pair remains rudimentary or unrecognizable. At no time are all of the arches present simultaneously for they appear in temporal succession and before the last pair appears the first two pairs have undergone regression. The third, fourth and sixth pairs are retained and utilized in the formation of the definitive pattern of major arteries. The manner in which this transformation occurs is schematically represented in figure 2.

Right Subclavian Artery Arising Distally and Passing Dorsal to Esophagus: This condition in man is variously designated as "retro-esophageal right subclavian artery," "right subclavian artery as last branch of aortic arch" and simply "anomalous right subclavian artery."

The anomaly in question consists of the right subclavian artery arising as the last major branch of the thoracic aorta, instead of from the innominate artery, and passing posterior to the esophagus on its course to the right shoulder region.

This variation was observed in uncomplicated form in four rat fetuses from vitamin A deficient mothers, and was the most commonly occurring anomaly of the several types encountered. All the published cases of the corresponding anomaly in man have not been collected and enumerated, but a minimal estimate would place the reported cases at several hundred (see Poynter[21]). Unquestionably this is the most frequently encountered congenital abnormality of thoracic arteries that may have clinical significance. Exactly as in the comparable

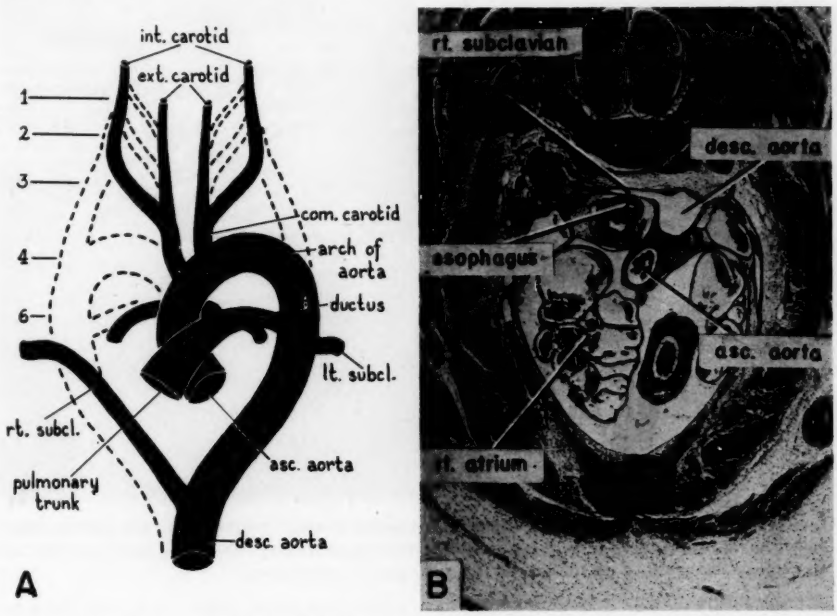

FIG. 3. A. Scheme of right subclavian artery that arises distally and passes dorsally behind esophagus. B. Photomicrograph of section through upper thoracic region of abnormal newborn rat showing distally arising right subclavian artery as it leaves descending aorta to cross midline behind esophagus.

malformations in man, the right subclavian artery of the rats arose as the last major branch of the thoracic aorta and crossed from the left to the right side of the midline by passing between the vertebral column and the esophagus (Fig. 3). The posterior aspect of the esophagus in the rat was not appreciably indented at the point at which it was traversed by the anomalous artery, but one would hardly expect a conspicuous degree of "notching" until the esophagus assumed full functional activity after birth. This anomaly of the right subclavian artery has been well known since the 18th century and was first explained developmentally by Wood in 1859.[21] It was described as a cause of dysphagia by Bayford in 1794,[22] but it is known now that pathologic manifestations of this anomaly are the exception rather than the rule. When crossing between the esophagus and the vertebral column, an anomalous right subclavian artery may press on the esophagus and reduce its

lumen, an impingement which can be demonstrated by roentgenographic examination of a barium-filled esophagus.[23] In case of dysphagia the abnormal subclavian artery can be divided and the esophageal pressure thereby relieved.[24] In a series of 610 cyanotic patients with a preoperative diagnosis of pulmonic stenosis, Blalock[25] observed a retroesophageal subclavian artery 26 times, and the anomalous vessel was used by him to complete an anastomosis between the pulmonary and systemic circulation.

Right-sided Arch of the Aorta: In five rat fetuses the right fourth instead of the left fourth embryonic arch was retained as the arch of the aorta (Fig. 4). The arterial pattern

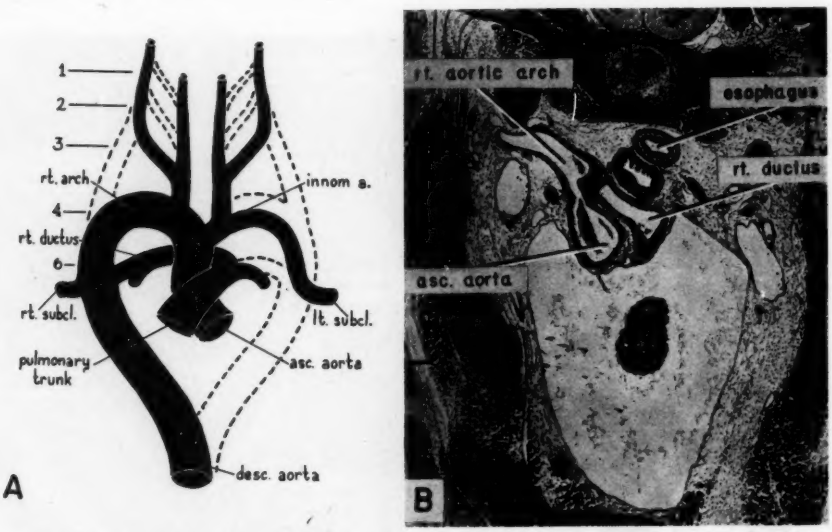

FIG. 4. A. Scheme of right aortic arch which is mirror-image of normal aortic arch pattern. Right-sided ductus arteriosus seen in this scheme and observed in several rats is only rarely seen in man. B. Photomicrograph showing right aortic arch and right ductus arteriosus.

in no two of these was quite alike, owing to variations in other arteries. Only one fetus had an arrangement of arteries that comprised a mirror image of the normal pattern: That is, the arch of the aorta, the ductus arteriosus, and the descending aorta were all on the right side of the midline; and the innominate artery arose as the first branch of the arch and passed to the left. This is not a common type of right-sided arch in man, but it has been recognized in some human cases in which the ligamentum arteriosum as well as the arch was on the right side.[26] A second variant of the right-arch pattern seen in one rat differed from the one just described in that it lacked a left pulmonary artery.

The right-arch-right-ductus pattern was varied further in one fetus which had a distal left subclavian artery arising as the last major branch of the right-sided aorta and coursing behind the esophagus to reach the left shoulder region. This situation represents a mirror-image of the distal right subclavian arising from the normal left-sided aorta. It is rare in man;[27] only about 10 cases have been recorded. This pattern in the rat fetus was modified by the absence of a left pulmonary artery and by the origin of both common carotid arteries from a single carotid trunk.

A fourth variant of the right-arch-right-ductus pattern was seen in one rat in which the

left subclavian arose, not from a left-sided innominate or directly from the right-sided thoracic aorta, but from the left pulmonary artery. This particular arrangement of arteries has never been described in man, but on theoretic grounds it could occur. The outstanding symptom of such a hypothetic case probably would be cyanosis limited to the left shoulder and upper extremity, since these regions would receive blood primarily from the right ventricle. No major vessel would course obliquely behind the esophagus; hence, notching or anterior displacement of the latter structure would not be expected.

The fifth type of right-arch-right-ductus anomaly, also found in only one rat, consisted

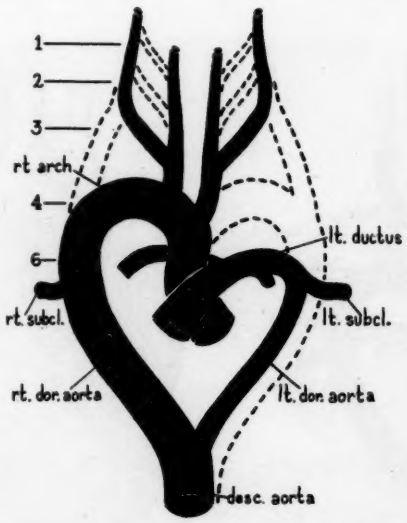

FIG. 5. Scheme of right aortic arch illustrating type which is relatively frequently found in man. Left ductus joins distal left subclavian which arises from left dorsal aortic root.

of a left as well as a right ductus arteriosus (sixth embryonic arch) with the former joining a distal left subclavian artery. This arrangement constituted a vascular ring which encircled the trachea and esophagus; with the right half of the ring formed by the right arch of the aorta, right ductus and right-sided descending aorta; and the left half by the left ductus and the remains of the embryonic left dorsal aorta. The left subclavian artery arose from the left half of the ring at the point where the left ductus joined the left aortic remnant. If after birth the left ductus had undergone the usual type of regression to form a ligamentum arteriosum, the arterial pattern would have closely resembled the right arch with distal left subclavian as described. This arrangement, right-arch-double-ductus, has not been recorded in man. It might easily have been overlooked, however, for if both the right and left ducti underwent regression after birth, the apparent resulting pattern would have been simply right arch with distal left subclavian. An additional ligamentum arteriosum on the right side could be missed in surgery or necropsy unless specifically sought, and in many of the reported cases the position was not stated. Of incidental interest in the present connection is the fact that in the rat fetus with right-arch-double-ductus, the right sixth arch (ductus and pulmonary artery) arose from the ascending aorta instead of from the pulmonary trunk. The most common type of right arch in man is one in which a single ductus

(ligamentum) arteriosus is present on the left side and attached to a distal left subclavian artery. In such cases the subclavian artery is usually described as arising from an "aortic diverticulum" (see Gross and Ware,[24] Fig. 3) which is in reality the remains of the left dorsal aorta of the embryo.

Two varieties of right-sided arch of aorta described relatively frequently in man were not found in the present group of rat fetuses and newborns. In both of these types a single ligamentum arteriosum passes from the pulmonary trunk to the left side. In one situation, alluded to above, the ligamentum appears to join a distal left subclavian which arises from a left aortic diverticulum (Fig. 5). In the other the ligamentum joins the left aortic diver-

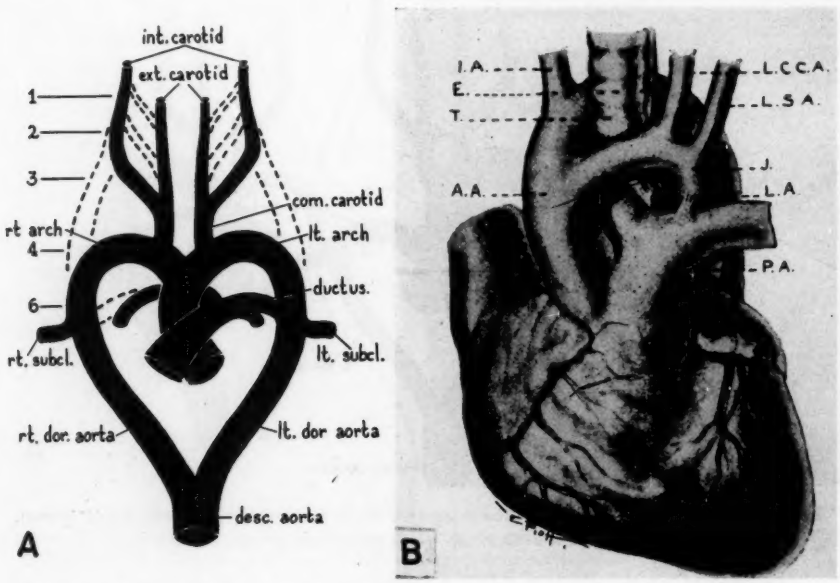

FIG. 6. A. Scheme of double aortic arch with left-sided ductus (ligamentum) arteriosus. B. Double aortic arch in child with respiratory difficulties. Child was successfully operated on by Dr. R. E. Gross.[22] Ascending aorta bifurcates into 2 branches; one passes behind esophagus; other arches in front of trachea. Two branches join to form descending aorta. Within vascular ring esophagus and trachea are compressed. AA-ascending aorta; E-esophagus; IA-innominate artery; J-junction of 2 aortic arches; LA-ligamentum arteriosum; LCCA-left common carotid artery; LSA-left subclavian artery; PA-pulmonary artery, and T-trachea. Ligamentum arteriosum was divided to allow pulmonary artery to be displaced forward. Anterior arch of aorta was divided to relieve compression of trachea. (Courtesy of Dr. R. E. Gross.)

ticulum which is connected with the descending aorta, while the left subclavian arises from a left-sided innominate artery. The latter group is characterized by a descending aorta which begins in the right side but then makes a sharp bend toward the left side and crosses the midline behind the esophagus to descend on the left side.[9, 26] In both instances the trachea and esophagus are, in effect, encircled by a vascular ring; but the left half of the ring is not patent since the ductus, or the ductus plus the remnant of the left dorsal aorta, underwent regression shortly after birth to form a fibrous cord known as the ligamentum arteriosum. The sharply oblique course of the descending aorta from right to left,

which occurs in both of these types of right arch, is apparently due to relative contracture of the ligamentum after it becomes sclerosed. The presence of an encircling ring about the trachea and esophagus, which may possibly be tightened by a relative or actual contracture of the fibrosed part of the ring, could well account for the fact that the two types of right-sided arch under discussion are those most likely to produce clinical symptoms. Chronic stridor and, less often, dysphagia may be caused by a persistent right aortic arch.[28] The diagnosis can be made during life by roentgenographic examination.[29] Surgical treatment of this anomaly has been attempted in a child who had difficulty in breathing and feeding since birth.[24] Right aortic arch is often associated with tetralogy of Fallot[9] and it

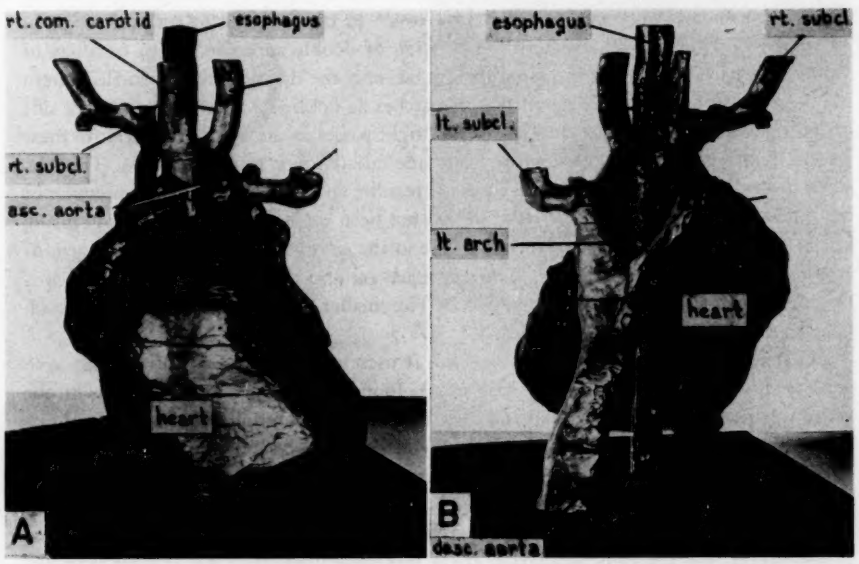

FIG. 7. Wax reconstruction model of heart and major arteries in rat with double aortic arch. A. Anterior view. B. Posterior view.

occurred in 144 of 610 cyanotic patients upon whom Blalock[25] operated. In such patients the operation is facilitated by the fact that the left subclavian artery is usually a long vessel which can be approximated to the left pulmonary artery without great difficulty.

Double Arch of Aorta: When both embryonic fourth arches are retained as connections between the ascending and descending aortae, the condition known as double arch is the result. This arrangement was found in two rat fetuses; but these differed in that one had the usual left-sided ductus arteriosus (Fig. 6A), whereas in the other both embryonic sixth arches had been retained, presenting the unusual situation of a ductus on either side. In both cases the bilateral arches arose from the ascending aorta, passed on either side of the trachea and esophagus, and reunited to form the descending aorta; thus a vascular ring was formed about the trachea and esophagus. In the animal with left-sided ductus the arches of the aorta were not of equal size, the left arch was somewhat the larger (Fig. 7). Also in this fetus the descending aorta lay on the left side; consequently, the right arch passed not only to the right of but dorsal to the esophagus in order to reach the descending aorta. In the case of double-arch-double-ductus the descending aorta was near the midline,

and although it veered toward the left side as it descended through the thorax, the two arches of aorta united almost directly behind the esophagus. In both instances the esophagus was displaced anteriorly in the region where these large arteries lay behind it, but it was not sharply notched, and there were no signs of constriction of either trachea or esophagus by the vascular ring in these fetal rats.

Double arch is a relatively infrequent anomaly in man, having been reported only about 40 times (to the knowledge of the present writers). In many instances it causes no adverse symptoms in the persons affected. However, infants have been described who had stridorous breathing, chronic cough, susceptibility to bronchopneumonia, head retraction, dysphagia and malnutrition.[30] The anomaly can be recognized by roentgenographic examination[31] and it was recently shown by Gross[32] to be amenable to surgical repair in children with clinical manifestations. Association of double aortic arch with tetralogy of Fallot is rare.[25] Of the types discussed for the rat, only the double-arch-left-ductus pattern has been described in man. Generally the two arches do not lie symmetrically on either side of the trachea and esophagus; but instead the right passes to the left and anterior to these viscera, both members then uniting in a left-sided descending aorta (Fig. 6B). The left-sided descending aorta seems to be a constant feature, and one wonders if the presence of the ductus (ligamentum) on the left side has not been the determining factor in causing a shift toward the left of what was at one time in the embryo a symmetric arrangement of arteries. Rarely in man are the two arches of equal calibre: the right and posterior arch is larger than the left in the ratio of about 5:1. The smaller of the two is frequently of such reduced size that it is considered stenosed.[26]

Absence of a Ductus Arteriosus: In four fetuses no complete embryonic sixth arch persisted; consequently, no ductus arteriosus was found connecting the pulmonary with the systemic circulation. In the absence of such a connection through the ductus, the heart theoretically could not develop proportionately in its right and left ventricles unless there were a persisting interventricular communication within the heart. The hearts of all four of these rats had moderately large interventricular septal defects. One of these hearts had the usual type of left-sided arch of aorta and descending aorta, discounting the absence of the ductus; but the right subclavian artery was quite unusual in that it arose from the pulmonary trunk at the origin of the right pulmonary artery. A similar anomalous origin of a subclavian artery was noted on page 715. Two of the animals without a ductus had a right-sided arch of aorta. One of these exhibited a mirror-image of innominate, carotid and subclavian arteries; but it lacked not only a ductus but a left pulmonary artery as well. The second pattern of right-arch-no-ductus differed in that the left subclavian artery arose distally from the right-sided descending aorta, and the right pulmonary arte y arose from the ascending aorta. In this case the right lung would receive in postnatal life oxygenated blood from the left ventricle. The remaining case of absent ductus possessed a double arch of aorta, with the two subclavian arteries arising from the respective arches. This arch pattern was further anomalous in that the ascending aorta and the pulmonary trunk were confluent at their origin, then separate for a short distance, only to reunite at the point of origin of the two arches of aorta. Such failure of complete partitioning of the embryonic truncus arteriosus to form separate pulmonary and aortic trunks is designated truncus arteriosus persistens. As applied to this rat fetus, the term must be qualified as "partial," since the pulmonary and aortic trunks were separate for a short distance (page 711). A single pulmonary artery, the right, arose from the separated segment of the pulmonary trunk; the left pulmonary artery was missing.

Absence of a functional ductus connecting the pulmonary and systemic circulation during fetal life is not compatible with normal development of the heart. Absence of a ligamentum arteriosum in postnatal life should be indicative of either (1) disproportionate development of the cardiac ventricles or (2) a congenital shunt between pulmonary and systemic circulation, e.g., an open interventricular septum. Therefore, when surgery is performed on the major arteries of the thorax, failure to find a ligamentum arteriosum connecting a pulmonary artery with the aorta may be of aid in evaluating conditions within the heart. If externally the ventricles appear properly proportioned, the possibility of an inter-

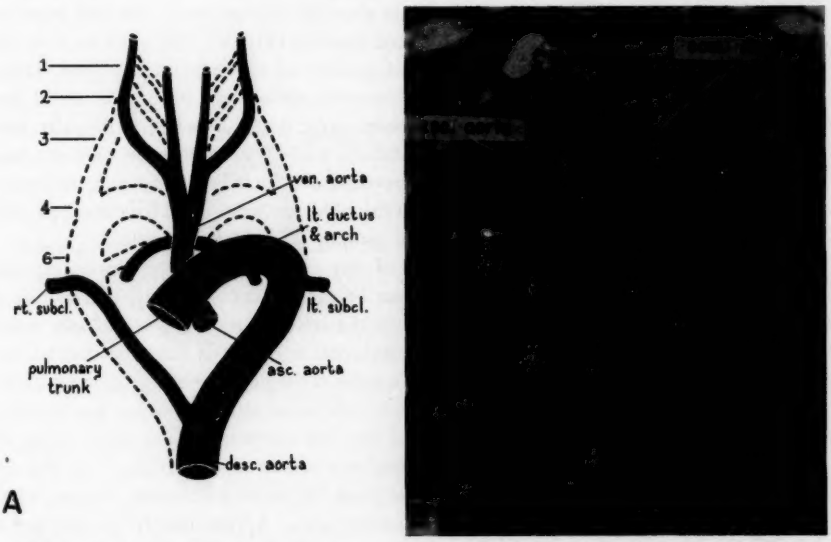

FIG. 8. A. Scheme of arterial pattern in one variety of absence of aortic arch (4th embryonic arch) seen in rats. Pulmonary trunk and enlarged ductus arteriosus serve as connection between heart and descending aorta. Small ascending aorta terminates by dividing into 2 common carotids; it does not communicate with descending aorta. B. Heart and large vessels of newborn child with respiratory difficulty and attacks of generalized cyanosis who died on 7th day of life. Small ascending aorta terminates in common carotid arteries and does not communicate with descending aorta. Pulmonary trunk is connected with descending aorta through ductus arteriosus. (Courtesy, Dr. Ralph Johansmann and Dr. P. S. Pierson.)

ventricular communication or an aortico-pulmonary fistula should be considered. In a large series of operations on patients with cyanotic congenital heart disease, Blalock[25] failed to find a ligamentum attached to the aorta in more than 100 instances. All these presumably had interventricular septal defects. The aortic arch pattern in these was that of right arch with the left subclavian from a left innominate, and the only ligamentum arteriosum ran from the left pulmonary to the left subclavian artery—a pattern not observed in rats. The mirror-image of this configuration, that is, left arch of aorta with a right-sided ligamentum joining an otherwise normal right subclavian artery, has been cited by Poynter[21] in four instances.

Absence of Arch of the Aorta: Failure of either embryonic fourth arch to persist as the main connection between the ascending and descending aortae is called absence of aortic

arch. In such cases either a sixth or a third embryonic arch, or both, must be retained to convey blood from the heart to the descending aorta. When an embryonic sixth arch alone serves as the arch of the aorta, the arterial pattern consists of an enlarged ductus arteriosus which arises from the pulmonary trunk and then continues directly into the descending aorta; and of an ascending aorta which is somewhat smaller than usual and terminated by giving rise to two common carotid, or two innominate arteries, or one of each. This general arrangement was found in two rat fetuses. In one the left ductus served as the arch, and at the point where it continued into the descending aorta, the left subclavian artery arose; the right subclavian artery arose distally from the descending aorta at a lower level and passed behind the esophagus to reach the right shoulder. Consequently, the only branches from the ascending aorta were the two common carotids (Fig. 8). The other rat with this general pattern possessed a mirror-image arrangement of the one just described. Hypothetically, had these rats had no other cardiovascular defect and lived after birth, they should have been cyanotic in all parts of the body except the head and neck. Actually, both had moderately large interventricular septal defects. Indeed, the ventricles could not have developed in their normal proportion if the interventricular foramen had not remained open; for the relatively much greater demands upon the right ventricle would have resulted in its enlargement, with a corresponding degree of atrophy of the left ventricle.

Similar anomalies, characterized by lack of any connection between ascending and descending aortae, have been noted in human beings. In one of the types, reported at least three times, the pulmonary trunk through the left ductus served as the only source of blood to the descending aorta. The left subclavian artery, as in the experimental rats, received blood from the right ventricle, since it arose at the juncture of the enlarged ductus with the descending aorta (Fig. 8B). The right subclavian artery, however, was a branch of a right innominate artery; the latter and the left common carotid artery were the terminal branches of the ventral aorta. A second type known in man differs from that just described in that both subclavian arteries arise from respective innominate arteries, which are the last and only branches from the ascending aorta. Approximately 10 instances of this pattern have been recorded in man (see Sewart[33]). Regarding the course of blood and clinical manifestations, the latter type of anomaly has many features in common with the infantile type of coarctation of the aorta. The absence of a connecting strand between the descending aorta and the first part of the left subclavian distinguishes absent arch from coarctation of the arch. Furthermore, it indicates that in the case of absent arch of the aorta the left embryonic fourth arch lost its continuity with the descending aorta prior to birth, probably early in fetal life. On theoretic grounds one would expect a patient with absent arch of aorta to exhibit cyanosis of the trunk and lower extremities but not of the head.[9] Cyanosis of the upper extremity would be variable, for either or both subclavian arteries may arise from the descending or the ascending aorta. Actually, such partial cyanosis has not always been observed. Cyanosis of the entire body and complete lack of cyanosis have been noted in children with this anomaly.[34]

Persistence of an Embryonic Third Arch Between Ascending and Descending Aortae: When the ascending aorta passes high into the neck, gives off separate external and internal carotid branches, then turns caudally into the descending aorta, the arch of aorta represents a persisting third embryonic arch. If there is no ductus on that side, the inferior (recurrent) laryngeal nerve arises from the vagus in the neck and goes directly to the larynx by passing under the third arch. This unusual situation was recognized in five

rat fetuses from vitamin A deficient mothers. No indication of a fourth embryonic arch was found in any of these. One animal had such a third arch on the left side; but on the right side there was an additional arch between the heart and the descending aorta, in the form of an enlarged right-sided ductus arteriosus connecting the pulmonary trunk with the descending aorta (Fig. 9A and Fig. 10). Since there were bilateral arches, this pattern constituted a vascular ring about the trachea and esophagus. The ring, however, was highly asymmetric and not constricting: its left half extended into the neck to the level of the larynx, but its right half rose no higher than the level of the third rib. The subclavian

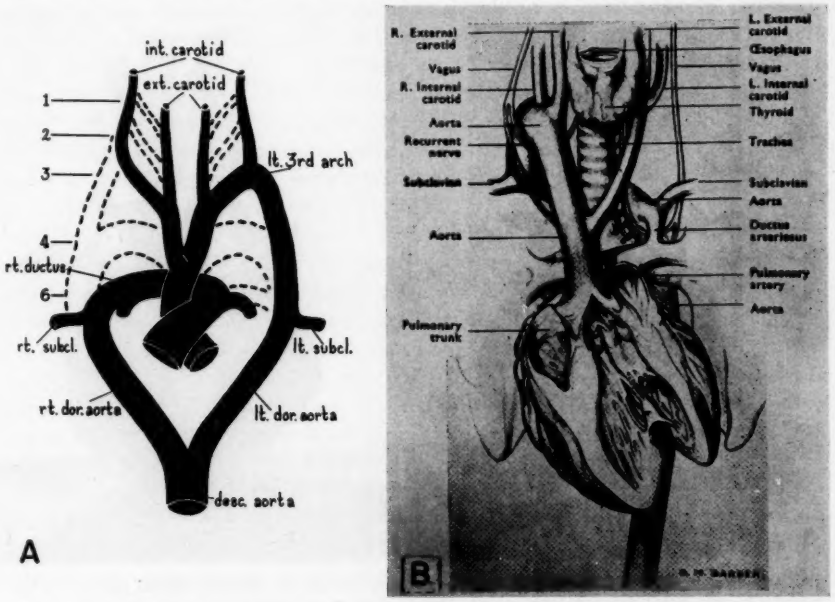

FIG. 9. A. Scheme of persistent left 3rd aortic arch which ascends into neck to level of larynx and gives off separate external and internal carotid arteries. No 4th arch persists on either side. Pulmonary trunk and enlarged right-sided ductus arteriosus constitute additional communication between heart and descending aorta. B. Drawing of postmortem specimen of heart and great vessels of child diagnosed during life as having aneurysm of common carotid artery. This arterial pattern represents mirror image of that shown in 9A; that is, right instead of left 3rd embryonic arch has been retained as arch of aorta. (Courtesy, Dr. T. E. D. Beavan and Dr. L. Fatti;[35] reproduced with the permission of the *British Journal of Surgery*.)

arteries arose from the respective arches (or dorsal aortae) and the right common carotid artery arose from the much elongated ascending aorta. There was no left common carotid.

At least one instance of a similar arch-pattern has been observed and reported in man. Beavan and Fatti[35] described a case which during life was diagnosed as aneurysm of the right common carotid artery, on the basis of a large pulsating mass on the side of the neck above the clavicle. At necropsy it was discovered that the pulsating mass was in reality the arch of the aorta connecting the ascending and descending aortae; and, since it was located in the neck and there gave rise to separate external and internal carotid branches, it was considered to be a persisting third embryonic arch. The arterial pattern in this case

was a mirror-image of that described in the rat above; the third arch was on the right side instead of the left. The left subclavian artery arose distally from the ascending aorta; but the left-sided ligamentum joined this subclavian artery, indicating that during fetal life the ductus served as an additional arch of the aorta, as was the case in the rat fetus. The left common carotid artery arose from the elongated ascending aorta (Fig. 9B). It is possible that other instances of third embryonic arch, represented by a pulsating mass on the side of the neck, have been mistaken for aneurysms or other vascular disease, particularly when no postmortem examination was performed.

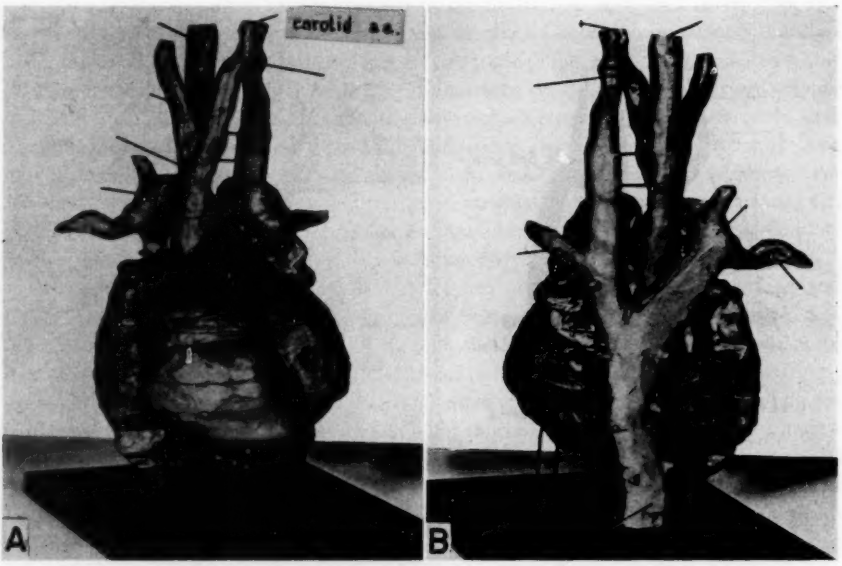

FIG. 10. Wax reconstruction model of heart and major arteries in rat with arterial pattern shown in Fig. 9A. A. Anterior view. B. Posterior view.

Four additional examples of persisting third embryonic arch were observed in the rat. In one the only connection between heart and descending aorta was a persisting left third arch that ascended to the level of the larynx; there was no ductus. The left subclavian artery arose from the left-sided descending aorta, and the right subclavian together with the right common carotid artery arose from an innominate artery which, in turn, came off the elongated ascending aorta. Left external and internal carotids originated separately from the crest of the left third arch. The three remaining instances of persisting third arch in the rat were identical and consisted of double third arches. No ductus and no common carotid were present on either side. Subclavian arteries arose from the dorsal aortae which formed the posterior limb of the respective bilateral arches. Pulmonary trunks were small in all, and this was especially so in one specimen in which the left pulmonary artery was missing.

Abnormalities of Pulmonary Arteries: Agenesis of the left pulmonary artery has been mentioned incidentally in six instances in the foregoing description of the various aortic arch anomalies. In five of these cases absence of the pulmonary artery was associated with agenesis of the left lung. It cannot be definitely stated that absence of the artery was secondary to agenesis of the lung, or the reverse, since no early stages of this condition

have been observed. However, one of the fetuses with missing left pulmonary artery had a well developed left lung, which was supplied through unusually large bronchial arteries. This case demonstrates that the lung and the pulmonary artery may be formed independently of each other. An additional fetus, not mentioned previously because it has no anomalies of the arches or heart, also had no left pulmonary artery and no left lung. It is mentioned here because it indicates that agenesis of the pulmonary artery is not necessarily associated with other cardiovascular anomalies.

Another abnormality of the pulmonary artery occurred in two animals in which the right pulmonary artery arose from the ascending aorta. In one of these a ductus continued beyond the pulmonary artery to join a right-sided descending aorta. Embryologically this type of malformation probably resulted from improper alignment of the aortic-pulmonary septum during the process of its formation,[19] so that the origin of the right sixth embryonic arch was included in the aortic rather than the pulmonary trunk. In connection with abnormalities of pulmonary arteries, it should be recalled that two instances of a subclavian artery arising jointly with a pulmonary artery from the pulmonary trunk have already been discussed (pp. 711 and 718).

Anomalies similar to those just described are known to occur in man. Anomalous pulmonary vessels have a possible significance in surgery even if they do not cause clinical symptoms. In recent years the increasing frequency with which the region of the hilus of the lung is approached surgically for pulmonary lobectomy and for repair of congenital defects, has made knowledge of such vessels important. Blalock[25] encountered agenesis of pulmonary arteries in nine cases operated for treatment of cyanotic congenital heart disease. Miller[36] described congenital absence of the right pulmonary artery in a newborn infant, but in the rats examined by us agenesis of pulmonary arteries was limited to the left side.

In regard to the aortic origin of a pulmonary artery, seen twice in our animals, it should be stated that Douglass[37] described four instances in which pulmonary arteries arose from the descending aorta. He also reviewed 23 additional cases of anomalous origin of pulmonary arteries from various sources, including subclavian and innominate arteries. No mention has been found of a pulmonary artery arising from the ascending aorta, but embryologic considerations and the fact that such an anomaly was noted in rats lends credence to the belief that its occurrence in man is a possibility.

Comment

None of the abnormalities described were seen in the controls which were sectioned and studied in the same manner as the experimental animals. Furthermore, such defects have not been described as occurring spontaneously or under other experimental conditions in the rat. Therefore, it seems justifiable to conclude that the cardiovascular anomalies of the young rats described here were induced by the experimental procedures to which their mothers were subjected. All the young with cardiovascular anomalies also had other malformations which were previously noted to be characteristic of a high percentage of the offspring of vitamin A deficient mothers.[16] The changes of the great vessels and of the heart occurred in association with anomalies of the eyes, of the genitourinary system and of the diaphragm with such regularity that they may be considered as part of the syndrome of malformations which results from these experimental conditions. However, cardiovascular defects were less frequently a component of the syndrome than were ocular and genitourinary defects; they were usually seen only in the more severely affected offspring.

These animal experiments provide an example of the influence of environmental

factors in altering development of the heart and great vessels. On the other hand, Sawin[38] demonstrated that genetic factors play a role in the determination of the aortic arch pattern in rabbits. These facts illustrate again that the embryonic development of an organ system may be similarly altered by either genetic or environmental factors.

Summary

Fetal and newborn rats from mothers fed vitamin A deficient diets prior to and during pregnancy exhibited some degree of malformation in 75% of the cases. Twenty-eight of 64 severely abnormal young studied after serial sectioning showed congenital cardiovascular malformations. These consisted of defects in the interventricular septum and in the aortico-pulmonary septum; and of various aortic arch anomalies, such as retroesophageal subclavian artery, right aortic arch, double aortic arch, absence and other variations of the ductus arteriosus and absence of a pulmonary artery. There were also several cases in which the fourth aortic arch was absent and the heart communicated with the descending aorta through the pulmonary trunk and an enlarged ductus arteriosus; in other instances the communication was affected through a persisting third arch which rose high into the neck.

Many of the cardiovascular anomalies observed in the rats closely simulated malformations observed in man; others have not been reported to occur in man but they are considered theoretic possibilities. If they are encountered in children, their interpretation may be facilitated by the description of these experimental results in the rat. It is emphasized that present clinical and experimental observations indicate that environmental as well as genetic factors may alter the development of the cardiovascular system.

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SPANISH ABSTRACT

Anomalías del Arco Aórtico y Cardíaco en Hijos de Ratas Deficientes de Vitamina A Correlacionadas con Anomalías Humanas Similares

Se tratan los factores etiológicos de anomalías cardíacas congénitas. Según prueba clínica parece que en algunos casos los factores genéticos y otros factores de ambiente pueden ser responsables por el origen de malformaciones cardíacas en los niños. En conexión con esto es de interés mencionar que se encontraron anomalías del arco aórtico y cardíaco en hijos de ratas alimentadas con dietas deficientes de vitamina A antes y durante el embarazo. En el corazón se observó la falta de cierre del septo interventricular. Entre las anomalías del arco aórtico estaban las arterias subclavias derechas saliendo a una distancia de la aorta descendiente y dorsal al esófago hasta alvanzar el hombro derecho; arcos aórticos dobles (cuarto); arcos aórticos derechos y muchas otras variaciones del patrón normal fueron observadas. Estas anomalías cardiovasculares estaban siempre asociadas con otras malformaciones congénitas, particularmente del ojo y del tracto genitourinario.

Elland and Bethesda Avenues

RELATION OF THE LET-DOWN REFLEX TO THE ABILITY TO BREAST FEED

By NILES RUMELY NEWTON, M.A., AND MICHAEL NEWTON, M.D.*
Philadelphia

THE let-down reflex is a psychosomatic mechanism which influences the expulsion of milk which has already been secreted. As a result of considerable investigation by Petersen and others[1-3] in cows, the mechanism can be postulated as follows: Nerves in the teat are stimulated by milking manipulations; these impulses are carried to the posterior pituitary gland which releases oxytocin. The oxytocin reaches the breast by the blood stream and acts on contractile cells surrounding the alveoli. Thus the contents of the alveoli are forced into the larger ducts where they are available to the sucking young or the milking machine. The experiments of Waller[4] and of Newton and Newton[5] indicate that the let-down reflex is operative in woman.

Sucking is probably the primary stimulus which sets off the reflex but the reflex is easily conditioned to such factors as the sight of the baby, scheduled time of feeding and breast preparations. Pain and distraction have been demonstrated to inhibit the reflex in cows and in woman, the inhibition being overcome by the administration of Pitocin.†[1,5]

The let-down reflex has long been recognized as an important factor in the success of milking cows. The purpose of this paper is to investigate whether it is an important factor in the success of lactation in women.

METHODS

The course of lactation was studied in 127 consecutive cases admitted to the maternity wards of the Hospital of the University of Pennsylvania. Mothers who attempted to breast feed were seen daily for the duration of their hospital stay and detailed records were kept of the symptoms of let-down,[4,6] and of engorgement, fissures and of the course of lactation. Most women stayed in the hospital 5 to 7 days after delivery, the first day being defined as starting at 12:01 a.m. of the day after delivery. Although the giving of advice about breast feeding was avoided, good rapport with the mother was obtained in almost every case.

Mothers were asked to report daily on the presence or absence of the following subjective symptoms of let-down:

1. Cramps or lower abdominal pain at the time of nursing. If let-down is functioning, the oxytocic principle should be circulating in the blood stream and should cause uterine contractions.
2. Dripping from the breast opposite to the one at which the baby was nursing. Dripping is probably caused by the contents of the alveoli being forced out into the already filled milk ducts.
3. Dripping at odd times, particularly upon sight or expectation of the baby. This is probably another sign of internal pressure suddenly exerted.
4. Cessation of nipple pain after the baby has sucked for a few seconds. The sucking baby builds up a high negative pressure which may cause pain.[7] This is lessened as let-down occurs and the vacuum is filled with milk.

An objective test of the degree of let-down was made in 37% of the breast feeding mothers.

* Assistant Instructor in Surgery and Harrison Fellow in Surgical Research, University of Pennsylvania Medical School, Philadelphia, Pa.

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† Parke, Davis and Company posterior pituitary preparation containing oxytocic substance 10 u./cc.

These represent a random sample of the total group. These tests were made at an average of 71 hr. after birth. The technic was as follows:

The baby was weighed before and after being taken to its mother. She was allowed to nurse him as long as she wanted. Within 10 min. after nursing had stopped, each breast was pumped with an electric breast pump for 5 min. Pitocin 0.3 cc. was then injected subcutaneously. After a 2 min. wait, each breast was pumped again for a further 5 min. The amount of milk obtained in each 5 min. period of pumping was measured. The amount of suction exerted by the breast pump was varied slightly from woman to woman owing to the varying amount of pain felt, but was constant before and after Pitocin in the same woman.

The Pitocin percentage is calculated from the following ratio:

$$\frac{\text{Amount of milk obtained after injection of Pitocin}}{\text{Total milk obtained by baby and breast pump}}$$

The milk pumped out in the post-Pitocin period roughly represents the milk that was in the breast but was not let down or made available to the baby. A low Pitocin percentage therefore indicates that most of the milk was let down as a result of the normal stimulation of the baby sucking and that the let-down reflex was functioning well. A high Pitocin percentage indicates the reverse.

Results

Table I shows the numbers of mothers in the various breast feeding groups. The study of the let-down reflex is confined to those mothers who actually breast fed. Successful breast feeders were defined as those who fed their babies entirely by the breast after the fourth day without bottle supplementation. Unsuccessful breast feeders were defined as those who continued to breast feed but who had to give supplementary bottles after the fourth day, and those who gave up the attempt to breast feed during their hospital stay. The latter amounted to 28% of the unsuccessful group. The successful mothers gave their babies more milk at an average fourth day feeding than the unsuccessful mothers. Supplementary bottles were provided for the mother to give the baby after the fourth day if the baby seemed hungry after being fed at the breast; if it was not gaining weight satisfactorily; or if the mother gave an average of much less than 60 gm. of milk at each feeding on the fourth day.

TABLE I

Nature of Breast Feeding Groups

	No. of Women	Percentage	Average Amount of Milk Given at 4th Day Feeding*†
			gm.
Successful Breast Feeders	53	42	69
Unsuccessful Breast Feeders	50	39	32
Mothers with Premature Babies	8	6	
Mothers Refusing to Breast Feed	16	13	
Total	127	100	

* Only mothers who continued to breast feed on the 4th day are included. The figures are obtained as follows: The average amount of milk given at each feeding on the 4th day was calculated by weighing each baby before and after each feeding. These average figures were then again averaged for all the mothers in the successful and unsuccessful groups.

† Highly significant difference; i.e., there is less than 1 chance in 100 of an equal or greater difference occurring by chance.

TABLE II

INCIDENCE OF SUBJECTIVE SYMPTOMS OF LET-DOWN IN SUCCESSFUL AND UNSUCCESSFUL BREAST FEEDINGS GROUPS*

	Successful		Unsuccessful	
	Total No. in Group	% Reporting Presence of Symptom	Total No. in Group	% Reporting Presence of Symptom
Uterine Pain During Suckling				
Day 1	16	50	10	50
Day 2†	50	64	39	38
Day 3	51	57	42	50
Day 4	53	47	43	49
Day 5	51	37	39	36
Day 6	42	26	30	20
Total All Days	263	47	203	40
Dripping from Opposite Breast during Suckling				
Day 1	16	13	11	0
Day 2	52	19	40	13
Day 3	51	63	42	52
Day 4	53	74	44	77
Day 5‡	51	86	38	74
Day 6‡§	42	95	30	67
Total All Days†	265	63	205	53
Dripping Before Suckling				
Day 1	15	0	11	0
Day 2	51	16	39	13
Day 3	51	47	43	35
Day 4	53	70	44	64
Day 5†	51	78	39	56
Day 6	42	86	30	73
Total All Days†	263	55	206	45
Cessation of Nipple Pain**				
Day 1	8	13	4	0
Day 2‡	35	66	23	48
Day 3‡	40	68	30	53
Day 4†‡	46	89	35	69
Day 5‡§	45	87	27	52
Day 6†‡	36	92	23	70
Total All Days§	210	72	142	58
Total All Symptoms All Days§	1001	59	756	48

* Variations in the group total are due to 4 factors: 1. Only those mothers are included who had actually put the baby at the breast. Some mothers were slow in deciding to breast feed; others discontinued it during the hospital stay. 2. On the first day, mothers were often interviewed before they had breast fed

Table II shows that the symptoms of let-down occurred more frequently in the successful than the unsuccessful breast feeders. A significant difference is found on at least one day for each of the four symptoms. In three out of four symptoms the incidence on all days combined is significantly higher in the successful group. The difference between the two groups in total average let-down symptoms is highly significant.

Table III indicates that unsuccessful breast feeders have a more erratic and less complete let-down. The Pitocin percentage of the unsuccessful breast feeders is significantly

TABLE III

INDICATION OF COMPLETENESS AND ERRATIC QUALITIES OF LET-DOWN REFLEX IN SUCCESSFUL AND UNSUCCESSFUL BREAST FEEDERS

(Nos. of Cases in Parentheses)

	Successful	Unsuccessful
Completeness		
Mean Pitocin percentage*	27 (27)	47 (18)
Erratic Qualities		
Range of Pitocin percentages	6–51	6–86
Standard deviation of Pitocin percentages	13	25
Average difference between 2 Pitocin percentages on same subject	14 (5)	24 (2)
Average coefficient of variation of amounts given at 4th day feedings*	32 (52)	57 (32)

* Highly significant difference.

higher than that of the successful breast feeders, which indicates less complete let-down to stimulation before the reflex was artificially set off. The greater range and standard deviation of Pitocin percentages, as well as the greater difference between two determinations in the same subject in the unsuccessful group, suggest that the reflex is more erratic in this group. This is confirmed by the significantly greater variation in amounts given at each fourth day feeding in the unsuccessful group. Erratic function of the let-down reflex would result in the baby's getting a lot of milk at some feedings and little at others.

In Table IV the mothers are divided into two groups according to the completeness of their let-down. Let-down is considered to be more complete or greater when the Pitocin percentage is 36% or less or when the incidence of positive let-down symptoms is greater than 60%. Let-down is considered to be less or less complete when the Pitocin percentage is greater than 36% or the incidence of positive let-down symptoms is less than 45%. Significant differences are found in the average amounts of milk given at each fourth day feeding. The incidence of marked engorgement is similar in both groups. Engorgement was measured clinically by the same observer and errors are likely to be consistent if they are present. The incidence of fissures is similar in both groups. A diagnosis of

the baby at all. 3. Occasionally a mother missed being questioned on one day. 4. The hospital stay varied from 5 to 7 days after the baby was born.

† Significant difference; i.e., there is less than 5 chances in 100 of an equal or greater difference occurring by chance.

‡ These combined differences for the same symptom on different days are highly significant.

§ Highly significant difference.

** Only those mothers who stated that they had nipple pain are included in these figures; some mothers said they had had no pain on some occasions.

TABLE IV

RELATION OF LET-DOWN TO MILK GIVEN ON 4TH DAY AND TO EARLY BREAST FEEDING COMPLICATIONS

	Cases	Marked Engorgement*	Nipple Fissures	Average Amount of Milk Given at 4th Day Feeding (gm.)
Greater Let-down				
Pitocin percentage 36% or less	22	64%	23%	59‡
Positive let-down symptoms greater than 60%†	37	54%	22%	62§
Less Let-down				
Pitocin percentage greater than 36%	16	38%	19%	39‡
Positive let-down symptoms less than 45%†	33	55%	18%	38§

* Marked engorgement was considered to be that degree of engorgement which was clinically assessed as 3+ or 4+.

† In these 2 groups either more than 60% or less than 45% of positive answers were to all questions regarding the presence of all let-down symptoms on all days.

‡ Significant difference.

§ Highly significant difference.

nipple fissure was made if the mother had a painful nipple and if there was objective evidence of a crack or bruised area on the nipple.

DISCUSSION

The presence or absence of let-down symptoms is a crude indication of let-down for three reasons:

1. Although Pitocin percentages seem to indicate that the let-down reflex operates in a quantitative manner, the let-down symptoms yield no indication of the degree of let-down. The quantity of dripping, the magnitude of the uterine contractions and the speed with which the nipple pain disappears are not measured. If the symptom was marked enough to come to the mother's attention, it was considered present and otherwise it was considered absent. The distortion that comes from this lack of quantitative data is suggested by the statements of the women who had had previous children within the last four years. None of those who had Pitocin percentages of over 36% remembered cramps upon suckling their previous child. Of those with Pitocin percentages of 36% or less, 44% remembered cramps. This suggests that their contractions were more severe. Unfortunately the presence of mild symptoms of let-down was given as much weight as the presence of marked symptoms. The effect of this is to minimize the differences between the successful and unsuccessful breast feeders.

2. The let-down symptoms are dependent on transient or abnormal states of the body or of lactation. Let-down symptoms may occur only on certain days and in certain women. Nipple injury and the perception of uterine contractions as pain are not necessarily normal phenomena, but may well be the results of a particular cultural environment. Dripping

cannot exist unless some milk is present. However, once there is milk in the breast, dripping occurs frequently at the beginning of lactation. As lactation progresses the let-down reflex seems to be more controlled. In some women, this control may come into play earlier than in others. Well established successful lactation is often completely devoid of let-down symptoms.

3. All the let-down symptoms are subjective in nature. Individuals differ in their ability to be observant and in their ability to resist suggestion. It is easy to see how some, being asked about nipple pains or other let-down symptoms for several days, would begin to become aware of symptoms of which they would otherwise not be conscious. At the start of the study mothers were asked whether they ever had a feeling of draught, or sudden heaviness or tingling which is sometimes reported to accompany let-down.[4] However, this question proved to be impractical because of its extreme subjectivity and the vagueness of the sensation.

The Pitocin percentage gives a more objective and more quantitative measure of let-down than the assessment of let-down symptoms. It is well known that injections of Pitocin make milk available in cows who have not let down their milk and in isolated perfused udders.[1,3] The following experiment was done to demonstrate that Pitocin has a similar effect in women. The subjects were mothers of premature infants who had never had the baby at the breast and whose breasts had not previously been pumped. Each breast was pumped for five minutes and then either Pitocin 0.3 cc. (six mothers) or normal saline 0.3 cc. (4 mothers) was injected and each breast was pumped for a further five minutes. Those in whom Pitocin had been injected gave an average of 55% of their total yield after the injection: those in whom normal saline had been injected gave an

TABLE V

VALIDITY OF PITOCIN PERCENTAGE

(No. of Cases in Parentheses)

	Pitocin Percentage 36% or less	Pitocin Percentage Greater than 36%
Percentage Reporting Let-Down Symptoms on Day of Pitocin Percentage Determinations		
Uterine pain	52% (17)	29% (17)
Dripping from opposite breast	59% (27)	35% (17)
Dripping before feeding	44% (27)	24% (17)
Cessation of nipple pain	72% (25)	55% (11)
Percentage Reporting Let-down Symptoms Occurring in Previous Lactation*		
Uterine pain	44% (9)	0% (6)
Dripping from opposite breast†	89% (9)	43% (7)
Dripping before feeding	75% (8)	57% (7)
Cessation of nipple pain	50% (6)	75% (4)
No. of wk. last child was breast-fed	18 (9)	10 (7)

* Only women who had had a child in the last 4 yr. are included in this series.

† Significant difference.

average of 35% of their total yield after the injection. The difference is statistically significant and shows that Pitocin helps to make available the milk that is in the breast.

Table V indicates the validity of the Pitocin percentage. Those who had percentages of 36% or less reported considerably more signs of let-down on the day the percentage was determined and remembered having more signs of let-down during their previous recent lactation periods; they fed their last child almost twice as long as those who had Pitocin percentages of over 36%.

The Pitocin percentage must be regarded as just a rough approximation of the actual milk not let down. Oxytocin seems to be rapidly destroyed in the blood stream[2] and thus the force of let-down is dissipated with time. As a result, a hungry baby can get out more milk than a breast pump applied some minutes later when let-down is no longer at its height. The hunger of the baby and the time elapsing between let-down and the first pumping were not completely controlled. These factors tended to make the Pitocin percentage variable and higher than it otherwise would have been. This helps account for the somewhat high Pitocin percentage of the successful breast feeders. Their average Pitocin percentage was 27% while only about 20% of the milk in a cow's udder remains after normal milking.[8]

Erratic let-down function is characteristic of cows who are drying up.[9] It is interesting to find this erratic quality in the unsuccessful breast feeders. It is possible that the erratic function may have special psychologic disadvantages for the baby. It may be frustrating to experience a gush of milk at one feeding and very little the next from the same breast.

The fact that more let-down symptoms and lower Pitocin percentages were found in successfully breast feeding women does not prove that let-down failure is necessarily a cause of lactation failure, but may only mean that the two are closely associated. However, there is a good possibility that let-down is a partial cause of lactation failure, and therefore it is worth examining ways in which let-down may be helped to function more adequately.

Pain, emotional conflict and embarrassment should be avoided as much as possible in the lactating woman as they inhibit the let-down reflex.[5,6] The pain of uterine contractions during suckling can be severe, often resembling labor pains. Nipple pain can also be acutely painful. The dread, fear and pain that these arouse may well be enough to inhibit let-down in some women. A drug to deaden the pain might occasionally be useful if administered before breast feedings. Newton and Newton found that a small quantity of alcohol made their subject less discriminating and more apt to let-down to the breast pump.[5]

Conditioning the let-down reflex may help it work less erratically. Pleasant stimuli such as the enjoyment of a favorite food or favorite music record could be prescribed to precede each feeding. Many cows get conditioned to the banging of milking pails, and we know one mother who started dripping when milk was served because during her hospital stay milk was served shortly before the baby was brought in. In cows the reflex is easily inhibited when unfamiliar sights and sounds accompany milking. Therefore, it would seem wise to breast feed in the same quiet place at each feeding until lactation is well established.

Waller suggests using manual expression of a little milk before feeding to set off the let-down reflex.[6] Stroking the nipple with clean tissue may have the same result.

The administration of Pitocin before feedings might be used occasionally in extreme cases. The resulting flow of milk might give the mother confidence in her ability to produce milk. It is quite possible that fear of inadequacy inhibits let-down. The baby who, in

turn, experiences a better flow of milk from the breast should take renewed interest in sucking.

As sucking stimulation is the primary stimulus in the let-down reflex, it is important that the baby be interested in sucking vigorously. A self demand schedule, which allows the baby to eat when it wants, probably ensures more vigorous sucking than the rigid schedule which often results in the baby's coming to the breast either sleepy or worn out with crying. A recent study[10] shows that bottle babies develop a weaker sucking reflex than breast babies. This suggests that it may be unwise to introduce the bottle to the child who must suck vigorously enough to set off the let-down reflex.

Summary and Conclusions

The existence and function of the let-down reflex was studied in 103 mothers who fed their babies at the breast while in hospital after delivery. Successful breast feeders reported a significantly higher incidence of symptoms of let-down than unsuccessful breast feeders. Successful breast feeders made a significantly higher proportion of their milk available to the baby and the breast pump before let-down was artificially induced with Pitocin. The let-down reflex functioned more erratically in the unsuccessful breast feeders. Methods by which the let-down reflex might be helped to function more adequately are discussed.

Acknowledgments

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Spanish Abstract

Relación del Reflejo "Let-Down" con el Poder de Dar el Pecho

Se estudió la existencia y funció del reflejo "let-down" en 103 madres que dieron el pecho a sus bebés mientras estaban en el hospital después del parto. Las que dieron el pecho con más éxito reportaron una indidencia de síntomas de "let-down" significativamente más alta que las que no tuvieron éxito. Las madres que tuvieron éxito en dar el pecho formaron una proporción mucho más alta de su leche disponible para el niño y la mamadera antes de que el "let-down" fuera artificialmente inducido con pitocina. El reflejo "let-down" funcionó más erraticamente en las madres que no tuvieron éxito con el pecho. Se discuten métodos con los cuales se puede ayudar a funcionar el reflejo "let-down" más adecuadamente.

227 South 45th Street

AUREOMYCIN IN THE TREATMENT OF RESISTANT BACILLURIA

By JOSEPH M. LOPRESTI, M.D., SIDNEY ROSS, M.D., AND MILTON B. RUBIN, M.D.
Washington, D.C.

WITH the advent of aureomycin and the demonstration of its wide antibacterial range against both gram negative and gram positive organisms and its lack of toxicity, together with the fact that resistant strains do not usually develop during the course of therapy, it was considered that this drug might well represent a valuable therapeutic aid in the treatment of urinary tract infection.

The studies of Herrell and Heilman[1] have shown that the amount of aureomycin excreted in the urine of patients receiving therapeutic dosage of the drug is far in excess of the amounts that would be required to inhibit the growth of micro-organisms frequently present in infections of the urinary tract.

Ten cases of urinary tract infections in children have been treated with aureomycin during the past few months at Children's Hospital (Table I). Of these, four were males and six females. Three patients were under 4 years of age while the others ranged from 4 to 8 years.

All these patients showed pyuria and most of them had symptoms referable to the urinary tract, e.g., dysuria, frequency, incontinence, enuresis and flank or lower abdominal tenderness. Nine of the patients received previous therapy without effect. The preceding therapeutic agents included mandelic acid, penicillin, sulfadiazine, and streptomycin.

In eight patients, the etiologic agent was Esch. coli, while the other two cases had mixed infections with Esch. coli and Staph. aureus. Sensitivity studies against Esch. coli, employing the method of Paine et al.,[2] were carried out in 8 of the 10 cases and in no instance was the organism found to be resistant to more than 1 μgm./cc. of aureomycin.

All the children treated in this series received aureomycin orally in a dosage of 30 to 60 mg./kg. body weight/24 hours in a four hour divided dosage schedule. When the child was unable to swallow an intact capsule, the drug was offered in chocolate syrup or syrup of cherry. No attempt was made to vary the pH of the urine; diet and fluids were permitted as desired. The duration of therapy varied from four to eight days. Daily urinalyses and several urine cultures were done during therapy. Intravenous pyelography was carried out in five patients; in four instances there was no demonstrable uropathy while in the remaining patient (Case 1) a bladder neck obstruction was observed.

Urine cultures in 9 of the 10 patients became sterile within 48 hours while the remaining one became negative in four days. In five patients, pyuria had disappeared by the end

From the Research Foundation of Children's Hospital, Washington, D.C.

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of the second day of therapy; the remaining patients showed no pyuria after four days of treatment. The subsidence of symptoms corresponded to the disappearance of the pyuria. At the onset of aureomycin therapy, fever was present in two children. The temperature in both cases returned to normal within 24 hours after treatment was instituted. The more dramatic of these was a Negro girl 2 years of age who had temperature elevations between 37.2 and 40°C. for 21 days prior to therapy. The temperature returned to normal 24 hours after aureomycin was started and the patient remained afebrile thereafter.

TABLE I

SUMMARY OF 10 PATIENTS WITH URINARY TRACT INFECTIONS TREATED WITH AUREOMYCIN

Patient	Urine Culture	Sensitivity of Organism to Aureomycin μg./cc.	Dosage of Aureomycin mg./kg./24 hr.	Duration of Therapy	Result
1. M. J.	Esch. coli	0.5	30 mg.	7 days	Negative culture in 43 hr. Recurrence in 1 wk.*
2. D. D.	Esch. coli	1.0	30 mg.	8 days	Negative culture in 48 hr.
3. D. W.	Esch. coli	1.0	60 mg.	8 days	Negative culture in 48 hr.
4. W. G.	Esch. coli	—	42.6 mg.	8 days	Negative culture in 48 hr.
5. C. R.	Esch. coli	1.0	45 mg.	5 days	Negative culture in 4 days.
6. L. D.	Hemolytic Staph. aureus and Esch. coli	0.5	42.6 mg.	5 days	Negative culture in 48 hr.
7. H. V.	Hemolytic Staph. aureus and Esch. coli	—	30 mg.	4 days	Negative culture in 48 hr. Recurrence in 2 wk.
8. E. W.	Esch. coli	1.0	50 mg.	8 days	Negative culture in 48 hr.
9. H. L.	Esch. coli	0.5	60 mg.	4 days	Negative culture in 48 hr. Recurrence in 1 mo.
10. H. H.	Esch. coli	1.0	30 mg.	5 days	Negative culture in 38 hr.

* Intravenous pyelogram revealed an anomolous obstruction of the urinary tract.

There have been three relapses in this series. One of these was in a Negro boy 8 years of age who had an associated anomalous bladder neck obstruction. Pool and Cook[3] have pointed out that the most important single factor in the efficacy of any treatment of urinary tract infections is the presence or absence of complications. Other pathologic conditions, such as anomalies, tumors, stones, residual urine or foreign bodies, must be cared for before the infection can be eradicated. Cultural reversals in the other two cases occurred in children who received aureomycin for a period of only four days. In these two instances, it was felt in retrospect that therapy was probably of insufficient duration. Attempts to get either of these two children back into the hospital for re-treatment were unsuccessful.

As regards untoward reactions, five patients developed vomiting during the course of aureomycin. This symptom occurred primarily in the older children and usually manifested itself within 24 hours after institution of therapy. As a rule it did not occur concomitantly with administration of the drug but most often during or just after a meal. Vomiting ceased when treatment was discontinued.

The following brief protocol serves to illustrate the course of events in one of the patients.

Case Report

D. D., a 5 yr. old white girl, was admitted to Children's Hospital with the chief complaint of urinary frequency. The mother stated that the child had had nocturnal enuresis since birth. Approximately 6 mo. prior to admission, marked frequency developed and at the same time the child became frankly incontinent of urine during the day. There had been no accompanying fever and the urine was described as "dark, strong, and cloudy." Gross hematuria had not been noted at any time. Three weeks before admission a urinalysis revealed the presence of pus cells and clumps in the sediment. The patient was given mandelic acid therapy for 2 wk. with no response. This was followed by penicillin therapy for 1 wk. with no effect on the subjective symptoms nor on the pyuria. A catheterized specimen grew numerous colonies of Esch. coli. The patient was hospitalized for streptomycin therapy.

On physical examination, the only positive findings were tenderness on palpation in the right flank and an ammoniacal dermatitis which covered both buttocks. Temperature was normal.

Urine analysis on admission revealed a 3+ test for albumin, a few red blood cells and many white blood cells with clumps. The hemogram showed a leukocytosis of 12,900 with 60% segmented neutrophils. Culture of a catheterized specimen at this time produced a profuse growth of Esch. coli (600-720 colonies/cmm.). An intravenous pyleogram made on the day after admission was reported as normal.

The therapeutic regime consisted of dihydrostreptomycin in a dose of 20,000 u. intramuscularly every 3 hr. On the 10th day after admission, the streptomycin was increased to 30,000 u. every 3 hr. At the same time, mandelic acid and sulfathiazole therapy were instituted. In spite of this vigorous treatment, the albuminuria and pyuria persisted and cultures of catheterized specimens continued to yield Esch. coli. Indeed, the colony counts increased to a point where they were innumerable and at this time the sensitivity of the organism to streptomycin was found to be 100 µgm./cc.

On the 14th day after admission, sensitivity studies revealed the organism to be susceptible to 1 µgm./cc. of aureomycin. Hence 2 days later all previous treatment was discontinued and aureomycin therapy was instituted in a dosage of 100 mg. orally every 4 hr. The therapeutic effect was prompt. Within 48 hr., frequency and incontinence had disappeared and a urine culture was sterile. Repeated urine cultures remained negative and the aureomycin was discontinued after 7 days. The patient was discharged after a 24 day hospital stay. In a follow-up examination 6 mo. later, the child was still free of symptoms and a routine urinalysis was entirely negative.

Summary

Ten children with urinary tract infections (eight of which were due to Esch. coli and two with a mixed infection caused by Esch. coli and Staph. aureus) were treated with aureomycin. The dosage ranged from 30 to 60 mg./kg./day in a four hour divided dosage schedule. The urine culture in 9 of the 10 patients became sterile within 48 hours while the 10th became negative in four days. There was a concomitant disappearance of pyuria and a subsidence of symptoms after initiation of therapy. Three of the patients, one of whom had a bladder neck obstruction, relapsed following discontinuation of aureomycin.

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SPANISH ABSTRACT

Aureomicina en el Tratamiento de Baciluria Resistente

Diez niños con infecciones del tracto urinario (ocho de los cuales fueron debidos a Esch. coli y dos con una infección mezcladada causada por Esch. coli y aureus estafilococo) fueron tratados con aureomicina. La dosis fué de 30 a 60 mg./kg. por día en un horario de dosis dividido en cuatro horas. El cultivo de la orina en 9 de los 10 pacientes se volvió estéril dentro de 48 horas, mientras que los otros se volvieron negativos a los cuatro días. Hubo un desaparecimiento concomitante de piuria y terminación de síntomas después del comienzo de la terapia. Tres de estos pacientes, uno de los cuales tenía una obstrucción en el cuello de la vesicula, recayó después de que se descontinuó la aureomicina.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

COMMUNICATIONS FROM DR. BORDEN S. VEEDER AND DR. WILLIAM PALMER LUCAS

INTRODUCTION

THE letter from Dr. Borden S. Veeder is one of the most important ones that has come to the Column. It presents the view that changes in the provision of medical care are currently taking place. Dr. Veeder suggests that the time has come to go beyond the debate about the advisability of such changes to a discussion of details. He then initiates such a discussion by stating his view that the capitation system of payment for medical services is incompatible with the continuation and development of pediatric practice as we know it in this country.

This is an extremely provocative statement. Certainly it is correct that the age group, under 16, with which the pediatrician deals, requires approximately twice as many visits per patient year as does the rest of the population. In order for a pediatrician to provide service at no higher level than that currently rendered by general practice, a capitation system would still have to allow a smaller panel and therefore a higher capitation fee to the pediatrician than to the general practitioner. Raising the level of care from that of general practice to that of the specialty further complicates the problem.

These are matters which are of concern to every pediatrician and to all those who are thinking about current trends in the provision of medical care.

The letter from Dr. William Palmer Lucas is concerned with the provision of well integrated services to the chronically ill child. Dr. Lucas has gathered statements from

many of the outstanding teaching services in the country and it is the editor's understanding that the quotations used in Dr. Lucas' letter have been edited and approved by the individuals concerned.

DEAR DR. HARPER:

As I look back over the years since the Column you now edit was started I feel it has done a great service. There is nothing so important as free discussion when it comes to subjects which from their very nature are muddled and confused. Naturally the viewpoint of some of the discussions has been biased, as it represented pro or con thinking in regard to controversial subjects. But the presentation of all sides, as the Column does, removes any stigma of bias from the Column itself, and the readers of PEDIATRICS are intelligent enough to form their own judgments.

To hold to the view that the approaching years will not see changes in the pattern of medical practice in the United States is to take the proverbial position of the ostrich. What these changes will be I am not wise enough to prophesy. I would hate to see bureaucratic controlled government medicine as I feel it will lead to a lowering of professional ideals, and to the deterioration of the medical care for children which I have seen make such tremendous strides over the last 40 years. It seems to me, however, that the time has come when we must begin to think of changes in a more detailed way and center some of the discussion on specific matters rather than continue the discussion along the general lines of those advocating and those opposing change. We must recognize the fact that changes have been and are being made in every phase of our social and economic life, and that the profession of medicine is not an isolated inviolable segment.

One of the questions that has bothered my thinking has been the effect of a nationally regulated method of payment for medical care on pediatric practice as it exists in this country.

Pediatric practice and the pediatrician in the United States is something quite different from pediatric practice and the specialist in pediatrics in Great Britain, Sweden and other countries where some form of national medical program exists. With us the vast majority of pediatricians are practitioners in private practice who limit their field to an age period, and their number is increasing by leaps and bounds. Last year, for example, nearly 250 new pediatricians were certified, and the Board has announced six examinations for 1950 instead of the usual three or four in order to take care of the applicants (there is a backlog of 500) who have finished their five year period of pediatric training. The Board has certified over 3000 and there are many hundred more in medical practice who limit their field to children. The practice of only a relatively few pediatricians in the United States is limited to teaching, hospital service and consultation, similar to the practice of the pediatric specialist in other countries. Thus the pediatrician in the United States is something unique in the general pattern of medical practice throughout the world.

Many years ago, based on practical experience in both methods, I expressed the view in a chapter in Brennemann's System that children received far better medical care from the pediatrician in private practice than it was possible to give through clinics and health centers, and that child health should be developed by the training of more pediatricians rather than the extension of public health activities. Some 20 odd years later I have found no reason or development to change this viewpoint, and more to the point it is the direction in which pediatrics has made such remarkable strides in the United States.

In Great Britain where medical care is not financed by insurance but from general taxation, the practitioner is paid on a capitation basis, while the specialist, including the pediatrician, in the hospital and clinics is in large part on a salary. In Sweden the practitioner is on a fee-for-service basis and the funds come from a compulsory insurance plan. There seems to be a general feeling that compensation for the practitioner on a salary basis is not desirable, except in unusual situations. Our present voluntary medical insurance plans call for payment on a fee-for-service basis, which was also the method adopted for the EMIC program, which was the first essay of the government into private medical practice. We find ourselves in agreement with Park and others that voluntary insurance plans eventually lead to compulsory insurance as evidenced by history. No insurance plan can survive which insures a disproportionate amount of the "poor risks" whether it be life, fire or health insurance, and this is one of the basic weaknesses of voluntary health insurance. Some of the most vociferous advocates of a national health program financed by compulsory insurance for this country also object strongly to the fee-for-service method of payment of the doctor. Their obvious alternative is payment on a capitation basis as in Great Britain. In much of the legislation so far proposed the method of payment is left very vague, and even to local choice which would probably produce a chaotic administrative situation, although from reports it seems to work in Switzerland where the administration is decentralized to the cantonments or states.

The problem I have been trying to think through concerns the effect of the method of capitation payment on pediatric practice as it now exists and is rapidly increasing in this country, and I have reached the opinion that payment by capitation might lead to the disappearance of the pediatrician and pediatric practice as we know it. Wherever pediatricians are located it has been amply demonstrated that the public prefers trained pediatric medical care for their children to that offered by the general practitioner or internist. Could families be split to permit this on a capitation basis? We doubt if it would be possible from an administrative angle. Even if this were done there remains the matter of the size of the panel. One composed of children would have to be much smaller than a panel including all ages. A third of the work of the general practitioner is with children, as disclosed by the "Survey." Thus 33% of the daily work would be with less than 20% of the total individual patient load of a panel. From this it can be calculated that the same amount of medical work would be required for a panel some 40 to 50% smaller if it were made up of children, as for a panel made up of all ages as it is in Great Britain. This would necessitate a different capitation fee. Could two practitioners, one in general practice and the other in pediatric practice, live and work harmoniously side by side, with a different capitation payment? I sincerely doubt it.

Therefore the conclusion seems to me to be that under any national medical program on an insurance or taxation basis that might eventually develop in this country the fee-for-service method of remuneration would probably be the only method under which pediatric practice as we now have it would survive.

Our primary interest is and has always been better medical care for children. This we have seen develop by great strides in the United States over a period of 40 years. There are a number of factors responsible, prominent among which are scientific advances, the result of pediatric research. One of the most important factors has been the better training and the tremendous numerical increase of pediatricians in private practice in this country, as contrasted with the pediatrician as a consultant in other countries. The pediatrician in practice has educated the public in demanding and recognizing good medi-

cal care, and his influence on the health of the community has been outstanding. Any form of a national health program that in its broad outline or in details would tend to eliminate the pediatrician in private practice must be carefully guarded against. Should this occur I fear the medical care of children will deteriorate, rather than improve as it has done over the last 20 years hand in hand with the tremendous increase in the number of trained pediatricians. It is a situation with which the younger leaders in pediatrics must be concerned. It is matters such as this that must be thought through now, so that if the situation ever develops that a national health program is enacted, the pediatricians will have a reasonable say in the matter based on arguments concerned with the best medical care that can be provided for children. To such arguments the politicians will listen. I am of the opinion that we must face facts, and that the time has arrived when physicians must think in a concrete way and be concerned with specific matters, rather than with such generalities as "free enterprise," the "American Way," and the like. It is for this reason I offer a viewpoint for discussion that seems to me to be important. Further I feel that in offering the opportunity of raising points like this for discussion the Column has an invaluable function.

(signed) BORDEN VEEDER, M.D.
St. Louis

DEAR DR. HARPER:

Teamwork is the present, most vital need in the treatment of the hospitalized child. In long-term illness, such as may be experienced in poliomyelitis with residual muscle involvement, it is especially important that the physician, the nurse, the ward maid, the teacher, the parents, the helpful volunteer, the physical and occupational therapist, and the social worker be integrally operating as a team.

The writer has just completed a study involving the main pediatric teaching centers in the country. The findings from the standpoint of real teamwork are, in many cases, disappointing—in some instances, shocking. At the top are such examples as the Department of Pediatrics at Yale, giving the finest type of physical and mental care. In such institutions the therapeutic influence of the teacher—from nursery school level through college preparatory—with parents and recreational therapists, parallels the excellent physical care of nurse and physical therapist. Such a team under the guidance of the physician works its wonders.

Other institutions exist which have no conception of the dynamics of such teamwork. In the worst of these each worker goes along in his own groove and the child patient and his parents are mentally torn asunder by conflicting impressions or lack of any direction. The result: long delays in each stage of treatment culminating in a permanent sense of frustration when the patient returns to his home. Eventual mental adjustment, under these conditions, may take months, even years. Why dwell on such failures!

Let us turn instead to those centers where we see the ideal carried out in practice. Here, if we are thinking in terms of the infantile paralysis patient, the pediatrician is the captain during the first period covering two or three weeks (except for bulbar cases and long, difficult primary stages); then the director of physical medicine or the orthopedist, who had had muscle evaluation and re-education experience, takes over to measure the degree of muscle involvement, to prescribe strengthening exercises and to attempt to predict the success which temporarily weakened muscles may eventually achieve.

After this most important screening, two or three weeks of intensive observation and care must be necessary. Toward the end, parents are trained to continue the exercises and the patient goes home for a period with plans for a return to a re-evaluation clinic or to the hospital at intervals. As an alternate course, the original screening may be followed by a period of six weeks' to six months' convalescence in another institution in the case of delayed recuperation or by discharge to the home. In such a situation the teacher can perhaps give the greatest therapeutic impetus to the child's day and the team, therefore, should be built around her direction. Children handled in this way make satisfactory mental adjustments, their parents understand the complete plan for the child, and the children "find themselves" at an early date.

This is the method carried out with such success at the Georgia Warm Springs Foundation under Dr. C. E. Irwin, Medical Director and Chief Surgeon, and Dr. Robert L. Bennett, Director of Physical Medicine.

Prior to the final discharge of the patient from the rehabilitation clinic the social worker should perhaps collaborate with the teacher to insure the use of all rehabilitating agencies in the community.

Under the plans set up by Dr. H. G. Poncher, Professor of Pediatrics at the University of Illinois Medical School, the undergraduate house staff and postgraduate level of physicians are all concerned in the in-service training of nursing, dietetic, occupational and physical therapy staffs. Even the attendants and ward personnel are drawn into the program. Dr. Poncher says: "I think it is extremely disastrous for any of the medical staff to verbalize a good program and then violate it in practice in the form of inconsiderate contact with patients. . . . An important cornerstone has been our program of occupational therapy which has been the central point around which the program has been developed. . . . The great hazard of setting up a special unit is the abandonment by the rest of the staff of their activities because of the existence of the unit. . . . Another feature is weekly staff conferences consisting of all personnel involved in the care of patients in which problems minor and major relating to such care are aired and threshed out, sometimes rather violently. The end result is, however, always better care for the patient and it serves to keep everyone cognizant of the general orientation of the department toward that care."

Dr. Charles A. Janeway, Professor of Pediatrics, Harvard Medical School, of Children's Medical Center, Boston, solves the problem in a different way. He writes: "Our major innovation has been the installation of a nursery school teacher in the children's ward. She works all day on a program which is constantly going on before the eyes of nurses and internes. This is having quite an effect, I think, on the total training program of doctors and nurses, as well as a tremendous difference in the general atmosphere of the ward. It also gives parents a chance to learn something about instructive play and recreation for their own children. In the chronic and convalescent wards, education and long-term projects of development are the main thing."

With his usual modesty, Dr. Janeway continues: "Although we have school, a Boy Scout group, and a regularly organized recreational program on our orthopedic ward, I think we still have quite a way to go before we are running a good over-all program such as the Army has in convalescent centers." Dr. Janeway realizes that centers may be temporarily limited in their development because of financial limitations but concludes: "The community will provide the school teachers if the staff will organize itself to see that a good all-round program is developed."

Dr. Stanley Cobb, Bullard Professor of Neuropathology, Harvard Medical School, tackles the problem realistically when he says: "Dr. Lucie Jessner, who is head of our Child Psychiatry unit, and I believe that the psychological difficulties and needs of the hospitalized child are strongly felt at the Massachusetts General Hospital. . . . The psychiatric service for children has as one of its study projects the emotional factor in hospitalization. The observation of chronically ill children on the ward has so far shown that in quite a number of cases psychological invalidism complicated or aggravated the illness . . . and that some of the children showed an arrest or retardation in their development (reluctance to learn, to grow up, in general preferred a dependent infantile state). . . . Some were even considered feebleminded by outside agencies but showed normal intellectual capacities when their emotional block was overcome. In others, neurotic and behavior disturbances were found (aggressiveness, denial of illness, rebellion against necessary restrictions, withdrawal, depression, irritability).

"Attempts at the prevention of psychological invalidism and at treatment are carried through by continuous discussions of the child psychiatrist with the pediatrician and the nurse in order to understand the child as a personality, his individual needs and motivation. The help in most cases was suggested (a) as individual psychotherapy for the child, (b) in an attempt to create a group spirit which would tend towards the maturing and productive possibilities of the child, (c) by providing activities for the child which would support the child's ego and self-esteem and would provide enticement into activities and possibilities for sublimation, (d) by consideration of the interpersonal relationships of physician and child, and nurses and child, and the children on the ward as a group, (e) by work with the family, particularly the mother and her attitude to the sick child. In general we have encouraged all ties to the outside world and to the home."

Dr. S. Z. Levine, Professor of Pediatrics, Cornell Medical School, gives a slightly different aspect of teamwork as carried out at New York Hospital. Here the program functions under the Institute of Child Development with Dr. Milton J. E. Senn as Director up to the end of this academic year and thereafter under Dr. Mary E. Mercer. Dr. Mercer gives this summary of the work: "Our experience indicates that in order to meet adequately the needs of the handicapped or sick child, we must all have a basic understanding of the well child. Hence our program is broken down into two main parts: (1) the teaching of normal emotional growth and development from infancy to adulthood, and (2) the application of this basic understanding to the special problems of the hospitalized child.

"The first part of the program includes orientation lectures on the normal emotional needs and behavior of children to house officers, medical students, nurses, and occupational therapists by a pediatrician with training in psychiatry. We feel that although this theoretical approach is fundamental, it must be accompanied by practical experience to have the fullest meaning. Consequently these professional groups participate for varying lengths of time in our New York Hospital Nursery School, where, under the guidance of a trained staff, they have an opportunity to see and deal with normal children in a full-day nursery school program.*

"The second part of the program is an attempt to take the understanding gained from the orientation lectures and the nursery school experience and apply it to the sick child on our pediatric floors. The pediatrician with training in psychiatry makes ward rounds

* We saw this in Van Pirquet's clinic in Vienna in 1925.

and is readily available to all these groups in the guiding and handling of the patients. Informal seminars are held on the individual children and are attended by house officers, medical students, occupational therapists, school teacher and volunteers. A unified plan of handling is worked out for the individual child according to his needs, insofar as it is possible to meet them in a hospital setting.

"Some of the changes which have evolved from the program follow: each patient is treated more as a total person than as a disease; greater leniency is evident in permitting children's parents to visit; a warmer relationship exists between the patient and the staff; fuller use is made of the occupational therapist and school teacher; each child is carefully prepared for any change in procedure; more often anesthesia is given in a patient's room in the presence of his mother before he is taken to the operating room; an atmosphere of friendly cooperation between all professional groups is marked which we feel stems to a considerable extent from a more unified understanding of the individual child and an all-out effort to meet his particular needs; and the children adjust to hospitalization more easily and many more of them actually come to enjoy their stay."

Dr. Howard W. Potter, Professor of Psychiatry, Long Island College of Medicine, writes that a psychiatrically trained pediatrician, Dr. Adelaide Frick, spends five half-days a week on the pediatric service at Kings County Hospital. "She appears to be making considerable headway in sensitizing medical students, internes, residents, and nurses to the emotional problems of sick children and their parents. The pediatric staff and Dr. Charles Weymuller, who heads the Pediatric Department at the Long Island College of Medicine, report that Dr. Frick has been a very worth while addition to their staff." Dr. Potter continues: "I think it would be very constructive if we could set up a group therapy project for the parents of children who are taken ill with poliomyelitis and bring these parents into the group as soon as we know what the rehabilitation needs of the children are going to be. I know from long experience that parents who are emotionally disturbed by the plight of their children simply cannot be expected to accept advice, no matter how good it may be, as to their management of the situation. It is not until their own emotional difficulties are resolved that they can be a constructive force in the rehabilitation of the child."

Dr. Bronson Crothers, Professor of Pediatrics, Harvard Medical School, emphasizes the same point when he says: "We tell the family that the child is not only a member of the family but the family is actually a part of the child from the developmental standpoint."

Dr. James Marvin Baty, Professor of Pediatrics, Tufts College Medical School, writes: "The period of hospitalization can be for the child a period of growth if all forces concerned work toward that objective . . . the speed with which children respond to a well-integrated, complete program for fostering good emotional adjustment and good, therapeutic, creative outlets is remarkable." At the Boston Floating Hospital the pediatrician, the director of nurses and the hospital superintendent top the pyramid of medical service. The team, consisting of psychiatrist, psychiatric social worker, clinical psychologist, teacher, play and occupational therapist, is selected for skill and emotional maturity. They must be wise in the concept of the child as a whole personality and have understanding of growth patterns.

Dr. Rowland Freeman, of the same institution, comments: "Graduate degrees do not necessarily qualify a person. They must be of a certain caliber, as far as possible without

prejudice, willing to work in all ways in all fields and with one another." "The base of the pyramid is the recreational therapy program with the convalescent playroom as its center. One-way glass walls are used to permit observation of child behavior; psychometric test procedures and, where needed, psychotherapy are available adjuncts. During the rounds and in conference where final diagnoses are discussed the pediatrician-in-chief is the one who constantly teaches about what the program can do for each child." Mrs. Edith T. Garfield, clinical psychologist here, comments: "The whole unit functions properly when it is an integral part of the hospital. When boards of trustees are able to have a look-see tour of this playroom filled with busy, creative children, they become convinced of the necessity to provide funds."

Dr. Baty, prime mover in many of the approaches to the problem at the Boston Floating Hospital, adds: "The primary purpose of the play-therapy unit was to minimize as far as possible the psychological trauma occurring during hospitalization. . . . It was not intended that children with gross behavior disorders or psychiatric disturbances should be sought or treated. . . . With the available personnel it proved impossible to evaluate the emotional and intellectual status of all patients admitted to the hospital. However, it is felt that all patients have been influenced by the activities of the psychiatric unit and about 65% of the patients have had personal attention from one or more of the members of the team." He concludes: "The program has proved helpful in the management of patients but it has been of even greater importance in developing interest in mental hygiene. The medical students, physicians, nurses and hospital personnel have become increasingly aware of emotional and intellectual development and their relationship to physiological function in health and disease."

Dr. L. Emmett Holt, Jr., Professor of Pediatrics, New York University-Bellevue Medical Center, reports that "team work in medical care is taken for granted. . . ." Regarding the social adaptation and education of the hospitalized child, the education is provided by city teachers on the wards. In addition, "the newly organized Children's Recreation Service, a voluntary charitable agency, is raising funds to provide for professional recreation workers some of whom serve to train a group of women volunteers who are designated as substitute mothers and work on our wards on a part-time basis."

Dr. Rustin McIntosh, Professor of Pediatrics, Columbia-Presbyterian Medical Center, where excellent teamwork supports the needs of the whole patient, also uses a recreation therapy group in the early stages "to keep children amused and prevent them from brooding over their troubles. As the child's clinical situation improves he may be given school work at his station and on further improvement may be sent to the special classroom on the twelfth floor suitably removed from the clinical services. . . . The work goes on constantly and it may even happen that a child patient will finish his formal grammar school course under our roof whereupon an appropriate celebration is staged. We do not have to advertise the value of the school service; it sells itself."

Equally well integrated programs under careful teamwork are evidenced at Haynes Memorial Hospital, Boston University School of Medicine, under Dr. William Malamud, Psychiatrist and Neurologist; at the University of Pennsylvania School of Medicine under Dr. Joseph Stokes, Jr., Professor of Pediatrics; under Dr. Irvine McQuarrie, Professor of Pediatrics, University of Minnesota Medical School; under Dr. Wilburt C. Davison, Professor of Pediatrics, Duke University; under Dr. Amos H. Christie, Professor of Pediatrics, Vanderbilt University; under Dr. James L. Wilson, Professor of Pediatrics and

Communicable Diseases, University of Michigan; under Dr. William A. Reilly, Professor of Pediatrics, University of Arkansas School of Medicine, Little Rock; under Dr. John A. Anderson, Professor of Pediatrics, University of Utah; under Dr. Myron E. Wegman, Professor of Pediatrics, Louisiana State University School of Medicine; under Dr. A. J. Ingram, University of Tennessee, College of Medicine, Asst. Dept. of Surgery, Campbell Clinic; under Dr. Jack R. Ewalt, Professor of Neuropsychiatry, University of Texas, Galveston; at the Unviersity of Kansas Medical Center, Kansas City, Kans., under Dr. Herbert C. Miller, Professor of Pediatrics; and at Johns Hopkins both in the Orthopedic services at Johns Hopkins Hospital under Dr. Francis Schwentker, Pediatrician-in-chief, and under Dr. Robert W. Johnson who carries the Orthopedic Service here and at the Children's Hospital School. (As the study progresses it will be possible to report upon the work in other centers.)

The programs of all these institutions show wide diversity of execution but in all instances the patient care is built around well integrated teamwork with the acknowledgment of the child's whole personality as the approach at all times. Dr. Reilly reports play therapy, quiet reading, guidance by teachers, and occupational therapy under good team-functioning in the acute stages of the disease at Children's Hospital, Little Rock, and in the convalescent home. "In both areas we are hampered by lack of bed space and not because of knowledge or interest." Dr. Wegman suggests careful consideration of service in school health work including conferences at schools concerning educational and vocational placements as a field worth further exploration. The University of Kansas secures the orientation of parents where possible by having the mothers stay with the children in available rooms or having the mothers and fathers room in as a part of the therapy. At Johns Hopkins play teachers are utilized even during the acute stage, and at the University of Utah the teacher is used to head up some 200 volunteers who extend her work on the wards and help in explaining the work with polio patients to the residents of Salt Lake City and of the whole state.

In a forceful presentation of the "Clinical Concept of Poliomyelitis," Dr. Edward B. Shaw, Professor of Pediatrics, University of California Medical School, San Francisco, and incoming president of the American Academy of Pediatrics, and Dr. Hulda E. Thelander summarize the situation as follows: "Above all is the necessity that some one physician maintain over-all direction of the patient. . . . Patients at times require the care of pediatrician, internist, orthopedist, the specialist in physical therapy, the occasional services of the surgeon, the bronchoscopist, the obstetrician, the urologist, the psychiatrist, the occupational therapist. Any one of several of these may best serve to direct the patient through his acute phase and his prolonged convalescence. It is not possible, however, to break up this care into numerous fractions which are not suitably integrated into adequate total care."* Children's Hospital, San Francisco, where Dr. Shaw and Dr. Thelander supervise pediatric care, has a well integrated service of volunteers, educators and the house staff. The attending physicians have available the aid of the psychiatric staff at the Child Guidance Center attached to the hospital. Joint rounds are made at intervals and psychiatric problems considered with other progress reports. In other words, all workers concentrate on the needs of the individual patient in order that, as Dr. Shaw so often reiterates to attendants, "We never let the polio patient down."

* Address delivered at the Areal Meeting of the American Academy of Pediatrics, Seattle, Wash., Sept. 13-15, 1948.

This program of evaluation is just begun. We hope to have the views of outstanding pediatricians, psychiatrists and particularly those specializing in physical medicine and orthopedics who are so vitally interested in the final steps in the treatment of the paralyzed child—not only in the hospital but in the rehabilitation centers which are coming into such prominence through local, state and national support. In this way our guidance will be more effective in every area where these children are being cared for.

(Signed) WILLIAM PALMER LUCAS, M.D.
San Francisco

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

ANNUAL REPORT OF THE FEDERAL SECURITY AGENCY

ON THE first of February, the Federal Security Agency submitted to the President and Congress its tenth annual report, for the fiscal year 1949, that is, the year ending June 30, 1949. The Administrator's Summary reviews briefly the activities of the Agency's constituent organizations.* The following excerpts are quoted directly from this summary report.

THE PUBLIC HEALTH SERVICE

No brief summary can cover the vast range of activities performed by the Public Health Service. It cannot suggest the close working relationships of the Service with State and local health authorities, voluntary health agencies, research and training institutions, hospital agencies, and professional organizations. Technical and consultative assistance, together with financial aid, from the Public Health Service has become so much a part of State and local health activity throughout the country that these services are taken for granted.

Much of the work of the Public Health Service, as in medical research and the development of new methods for the control of serious diseases, is necessarily long-term. But results are constantly being obtained and more widely applied in state and local programs which directly affect the lives of millions of Americans.

During the fiscal year, for example, Public Health Service teams took chest x-rays of more than 1.5 million persons in tuberculosis surveys sponsored by some of our large cities. In 35 States, more than 150,000 school children had their teeth examined and treated with sodium fluoride solution to prevent decay. Public Health Service dental health teams provided these services in demonstrations for State and local health departments and private dentists. More than 1500 public health workers from all over the Nation and from 37 foreign countries received special training at the Service's Communicable Disease Center in Atlanta, Ga., and 640 of these were trainees from public and private laboratories, who desired training in the performance of diagnostic tests.

Besides these and other special services in aid to state and local health agencies, the Public Health Service continued its fundamental programs of health protection and promotion. The Nation's official vital statistics were collected and compiled, thus making available the basic data on which national health problems can be defined and progress measured. Foreign and interstate quarantine activities ensured protection against the introduction of epidemic diseases from abroad and their spread from state to state. Through its system of standards, inspection, and licensing, the Public Health Service

* The Administrator's summary and separate reports of the Agency's constituent organizations are available at nominal cost from the U. S. Government Printing Office, Washington 25, D.C.

ensured the interstate sale of safe and potent vaccines, serum, and other biologic products. . . .

State and local appropriations for general public health work, tuberculosis, venereal diseases, cancer, and mental health were the largest in history. Federal grants-in-aid to the States for these purposes also were larger, totaling $36.4 million, excluding grants for hospital construction.

Heartening gains were also made in the hospital construction program. By the end of the fiscal year, all states and territories had completed their surveys and plans, and 791 projects had been approved for grants. Of these, 35 projects had been completed and 355 were under construction. These projects represent 450 health centers and more than 38,000 hospital beds to be added, chiefly in rural areas, to the Nation's health resources. The total amount of construction so far approved will involve some $150 million in Federal funds. Under the Hospital Survey and Construction Act of 1946, however, this sum represents only one-third of the total cost of these facilities; the remainder is contributed by the state and local sponsors of the projects.

Another significant advance is the increase of regional planning for state and community hospital service, including nursing service. The hospital construction plans of the states are based on the concept that hospitals should be located so as to provide facilities for a "hospital service area," that is, for several communities. Many professional and civic groups have expanded this concept to plan for regional service, as well as for regional facilities. Under such plans, several hospitals or communities may agree to pool their medical, hospital, and nursing services to care for a larger group of people than would be possible through separate programs. Although few such regional services are as yet in operation, the Public Health Service has received so many requests for consultation in this field that it is evident the professions and the public are becoming convinced that joint planning and action for the provision of medical, hospital, and nursing services are essential. . . .

The continuing need of additional Federal aid to the states for local health services underscores, in general, the difficulties under which our communities are trying to set up and expand their public health departments. More or better-staffed local health units are needed in almost every part of the country. The fact that only about 1600 of our 3000 counties and 250 of the largest cities have full-time health units, and that less than 5 percent of these are fully staffed, is one measure of how far we are from our goals. Congressional action to increase Federal funds for this purpose is urgent. . . .

The continuing financial crisis in medical education, including the training of physicians, nurses, dentists, and graduate public health workers, points up another critical need in the Nation's health services. Shortages of trained personnel in all fields continue. Conferences with medical educators and professional leaders during the past year brought out the urgent need for general Federal aid in this field. Not only must our existing annual supply of professional workers be maintained, but also the future supply must be increased to meet increasing needs.

Legislation was introduced in the Eighty-first Congress proposing grants to accredited medical, dental, nursing, and public health schools, for scholarships for qualified students, and for the construction of teaching facilities. At the close of the fiscal year, the proposed bills had not been acted upon. . . .

The research potential of the Nation has been increased by Federal programs of aid to medical research, administration by the Public Health Service. If we are to broaden

our Nation-wide research effort, there must be an adequate supply of research facilities and of well-trained scientists.

During the fiscal year, the Public Health Service allocated approximately $2 million in grants and contract authorizations to seven institutions for the construction of additional research facilities. These expanded facilities will be devoted to research in cancer, cardiovascular diseases, mental and nervous diseases. The Clinical Center of the National Institutes of Health, now being constructed at Bethesda, Md., also will add to the Nation's facilities for basic and clinical research in diseases that take the highest tolls of life and cause the largest volumes of disability.

Through the research fellowships program of the National Institutes of Health, the Nation's supply of scientists in the medical fields is being steadily increased. In 1948-49, 432 fellows were appointed to receive advanced research training in institutions of their own choosing. Since 1945, more than 300 other scientists have completed their fellowships. . . .

The Children's Bureau

The high birth rate of recent years presents problems not only for the educator but for the child health and welfare authorities as well. Since 1940, the number of children under the age of 5 has increased by more than 40 percent, and between the ages of 5 and 9, by more than 20 percent. For the fiscal year, grants-in-aid by Congress in support of these Federal-State maternal and child health and child welfare services, administered under the general supervision of the Children's Bureau of the Social Security Administration, amounted to $22 million.

Of the Federal money in this field, $11 million is earmarked each year for grants to the states for maternal and child health services. These services range all the way from prenatal clinics, public health nursing services, and well-child clinics to immunization services and examination of children of school age by physicians and dentists. On a limited basis, many states also provide medical and dental care for some expectant mothers and also for a considerable number of children.

During the current year, well over 150,000 expectant mothers attended the medical clinics operated by these services, and more than 220,000 received public health nursing services during pregnancy. Some 640,000 infants and children of preschool age had the benefit of medical supervision at well-child clinics, and over a million received public health nursing services. Physicians' examinations of school children totaled more than 2 million, and inspection by dentists or dental hygienists ran half that number. Public health nursing reached nearly 2½ million, and nearly 3 million immunizations against smallpox and diphtheria were given.

Most of these areas of activity showed significant increases during the year. But it is fair to say that, throughout the whole Nation, the funds available were so limited as to prevent the services from reaching more than a fraction of the mothers and children who stood in genuine need of them.

For the Federal share in services to crippled children during the fiscal year, Congress appropriates $7.5 million each year. An estimated 175,000 children received diagnostic treatment services under these Federal-State programs. About 30,000 were hospitalized; nearly 5000 were cared for in convalescent homes. Reports toward the end of the fiscal year showed a waiting list of 30,000 who needed care but for whom no funds were available. To ease this situation Congress made a supplementary appropriation of $750,000, as of June 30, 1949, for grants to the states.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

CONTROL OF COMMUNICABLE DISEASES IN MAN

IN ANY community, the problem of the spread of disease, directly or indirectly, from one human being to another is a concern of every physician who cares for children. All pediatricians, therefore, will welcome the publication of a new version of the most authoritative statement of accepted procedures in this field—the seventh edition of *The Control of Communicable Diseases in Man.**

This document is a report of the Subcommittee on Communicable Disease Control of the Committee on Research and Standards of the American Public Health Association. Haven Emerson, M.D., is Chairman of the Subcommittee. In addition to the distinguished epidemiologists who are members of the Committee itself, collaboration was given by the Academy of Pediatrics, whose representative was Dr. Archibald Hoyne, the Pan-American Sanitary Bureau, the Department of National Defense, the Ministry of Health of Great Britain and the World Health Organization.

The report has been adopted as official by many foreign countries, and many states lean upon it heavily for their regulations. It is pointed out, however, that:

"Inasmuch as the laws under which various local, state and national boards and departments of health operate require differences in the legal phraseology of rules, regulations, or sections of sanitary codes dealing with the control of communicable diseases, formal regulations under each disease are not given. As the report is at present submitted, any health officer, board of health, or legislative body having the power to make rules or regulations, or to enact sections of sanitary codes dealing with the control of communicable disease can, by reference to the description of the disease and recommendations for methods of control herewith presented, prepare the necessary text upon which the educational and administrative acts of the health officer will be based."

At the outset, the report defines a great many terms commonly used in this field. Certain of these definitions are here reprinted because they are so often confused by both laymen and medical practitioners:

"Contact—A 'contact' is any person or animal known to have been in such association with an infected person or animal as to have been presumably exposed to infection.

"Isolation—The separation for the period of communicability of infected persons from other persons, in such places and under such conditions as will prevent the direct or indirect conveyance of the infectious agent from infected persons to other persons who are susceptible or who may spread the disease to others. This applies also to animals.

"It is considered necessary to require strict isolation of the patient for the period of communicability, and to quarantine or immunize contacts, in certain diseases, notably smallpox. However, in some other diseases, such as poliomyelitis, isolation of the patient has but little effect in limiting the spread of the disease.

"In diseases of this latter sort the patient must be regarded as a potential source of

* Control of Communicable Diseases in Man, ed. 7, New York, American Public Health Association, 1950.

infection and suitable precautions must be taken, even if these barriers to transmission of the disease are but partially effective. Uncertainty as to the exact duration of the period of communicability does not justify neglect of reasonable isolation measures but rather adds to the obligation to educate patients, the family, and the attending physician in the advantages to be had from separating the sick from the healthy. Precautionary measures should be taken voluntarily when the presence of a communicable disease is suspected and before a diagnosis is established, after the official period of isolation is past, and generally during the epidemic prevalence of such diseases in the community.

"When the term 'isolation' is used in connection with such diseases as the common cold, influenza, chickenpox, mumps, and the pneumonias, it is to be understood that the establishment of isolation is not, under ordinary circumstances, a necessary or practicable procedure for official requirement or enforcement, but a practice to be instituted under the direction of the attending physician, and its duration to be generally, if not exclusively, at his discretion.

"Isolation of a patient with a communicable disease from visitors is often to his own benefit so far as it reduces the likelihood of additional and complicating infections, as well as being a protection to others.

"Quarantine—(1) Complete quarantine is the limitation of freedom of movement of such persons or animals as have been exposed to a communicable disease, for a period of time equal to the longest usual incubation period of the disease, in such manner as to prevent effective contact with those not so exposed.

"(2) Modified quarantine is a selective, partial limitation of freedom of movement that is determined, commonly on the basis of known or presumed differences in susceptibility, but sometimes because of danger of disease transmission. It may be designed to meet particular situations. Examples are exclusion of children from school or exemption of immune persons from provisions required of susceptible persons, prohibition of contacts from acting as food handlers, or restriction of military populations to the post or to quarters. This may apply to domestic animals as in the case of dogs immunized against rabies.

"(3) Surveillance is the practice of close supervision of contacts without restricting their movements. This may apply to domestic animals also.

"(4) Segregation is the separation for special consideration, control, or observation of some part of a group of persons from the others, to facilitate the control of some communicable disease. Removal of susceptible persons to homes of immune persons, or the establishment of a sanitary boundary to protect uninfected from infected portions of a population are examples. This may apply to domestic animals also.

"Placarding—This official procedure under local or state authority consists of posting a warning notice upon the door or entrance to living quarters of persons isolated because of communicable disease. The object of such placarding is primarily to keep unauthorized persons from entering upon the premises during the period of communicability in the isolated patient. Such placarding may incidentally protect the patient against additional or secondary infection by visitors. Its use may have some educational value.

"Placarding, as practised in the United States, does not aid significantly the efforts of a health department to control the acute communicable diseases ordinarily spread directly from person to person (chickenpox, mumps, pertussis, measles, diptheria, scarlet fever, anterior poliomyelitis, meningococcus meningitis, pneumonia, tuberculosis, gonorrhea, syphilis); consequently it is not recommended in the control of these diseases.

"Placarding has definite disadvantages: it is difficult to enforce, it may be a deterrent to reporting, it is costly in transportation. The most serious objection is the loss of time of public health nurses and other health department employees that should be devoted to practical instruction in the observance of isolation and concurrent disinfection at the bedside of patients suffering from the more serious communicable diseases."

Extension of knowledge of infectious diseases is illustrated in added pages and new diseases covered. These include many of the infections which have become important since the war with the return of troops from all over the world. The section on rickettsial diseases has been broken up and the discussions of many of the individual diseases expanded considerably. Rickettsial pox, which is being reported with increasing frequency, earns a section for itself. Homologous serum jaundice, enterobiasis and histoplasmosis are newly discussed diseases which are of particular interest to pediatricians.

As in the previous edition, scarlet fever is considered as one form of streptococcal sore throat and no distinction is made in regard to control procedures. Quarantine is considered unnecessary and isolation of the patient is recommended until clinical recovery but at least seven days from onset. Other diseases treated in separate sub-headings under the common heading of hemolytic streptococcal infections are erysipelas and puerpural infections.

Detailed discussion could well be given of many other common infections but every practitioner will want a copy of this valuable manual for himself and for the guidance of his community.

NEWS AND ANNOUNCEMENTS

The National Foundation for Infantile Paralysis is offering fellowships to physicians for one academic year of study leading to a Master of Public Health degree at a school of public health approved by the American Public Health Association.

Eligibility requirements include United States citizenship, graduation from a Class A school of medicine, completion of an interneship of not less than one year, license to practice medicine in one or more states and sound health.

Financial benefits are flexible and will be arranged according to individual needs. Candidates will be selected competitively by the Committee on Fellowships in Public Health.

In accepting a fellowship each recipient must agree to work as a public health officer in a state or local health department in the United States or its territories for at least two years.

The Foundation is offering also one to three year clinical fellowships in physical medicine to physicians who wish to prepare for certification by the American Board of Physical Medicine.

Eligibility requirements are the same for fellowships in physical medicine as for fellowships leading to a Master of Public Health degree.

Fellowships are limited to those of 40 years of age or less. Candidates will be selected competitively by the Committee on Fellowships in Physical Medicine, composed of members of the profession certified by the American Board of Physical Medicine.

In accepting a fellowship each recipient must agree to practice as a specialist in physical medicine in the United States or its territories for a minimum of two years, and must have completed three years of clinical study. Both of these requirements are necessary to qualify for Board certification.

Additional information and applications may be obtained from Professional Education Division, The National Foundation for Infantile Paralysis, 120 Broadway, N.Y.

* * *

On Nov. 14, 1949, the Executive Board of the American Academy of Pediatrics approved the following recommendation of the Committee for the Study of Radiation Effects in Childhood concerning the use of radioactive isotopes:

"No research study with radioactive isotopes should be undertaken on pregnant women unless: 1. It cannot first be done on animals; 2. The study is approved by the Committee for Human Use of Radioactive Isotopes of the A.E.C."

The recommendation was made because of the ready availability of certain radioactive isotopes at present.

The purpose of this communication is that this Committee believes the profession as a whole is unaware that it is now possible for an individual obtaining isotopes from a cyclotron to be the sole judge of how these substances are to be used.

* * *

COMMUNICATION RE THE SIXTH INTERNATIONAL CONGRESS OF PEDIATRICS AMERICAN COMMITTEE

Official delegates to the Congress representing the four national pediatric organizations are as follows: American Academy of Pediatrics: Drs. Rustin McIntosh and Oliver L. Stringfield; American Medical Association, Section on Pediatrics: Drs. Margaret M. Nicolson and Adolph G. deSanctis; American Pediatric Society: Drs. L. Emmett Holt, Jr., and A. Ashley Weech; Society for Pediatric Research: Drs. Henry L. Barnett and Robert Ward.

The members of the American Committee will represent the United States at the Executive session of the Congress. They will also be glad to assist in any way possible those who plan to attend or participate in the Congress or the Scientific Exhibit.

The date for registering participation in the Congress has been deferred to April 22, 1950. Participants must register with the American Express Comany, Inc., Sihlporteplatz 3, Zurich, or their agencies or correspondents in the different countries.

The International Union against the Venereal Diseases will hold its 27th General Assembly in Zurich, Switzerland, July 28-Aug. 2, 1950, at which Assembly a joint session of delegates of the IUVD and of the 6th International Conference of Pediatrics will be held on July 28. Many of the pediatricians attending this Congress and syphilologists and others attending the Union's Assembly will welcome the opportunity of being present at this meeting.

At the Annual Meeting of the American Academy of Pediatrics in San Francisco, the Chairman of the Committee on Latin American Affairs was authorized to solicit money for the purpose of offering again the Latin American Scholarships which had been discontinued because of war conditions.

The Chairman of the Committee reports that the first of these $2000 Scholarships has come from the M & R Dietetic Laboratories, Columbus, Ohio.

* * *

The American Board of Pediatrics, Inc., announces that oral examinations will be held at:
Cincinnati—May 5, 6 and 7, 1950
San Francisco—June 30, July 1 and 2, 1950
Chicago—October, 1950
Boston—November, 1950
Complete information concerning further details may be obtained by addressing: The Executive Secretary, 6 Cushman Road, Rosemont, Pa.

* * *

The following candidates were certified by the American Board of Pediatrics:

RICHMOND, VA.—FEB. 10, 11 and 12, 1950

Adams, Myron John, 103 Fairridge Drive, Kingsport, Tenn.
Bessman, Samuel Paul, Children's Hospital, 13th and V Sts., N.W., Washington, D.C.
Bonner, John C., 95 Rutledge Ave., Charleston, S.C.
Christensen, Thomas A., 6905 Baltimore Blvd., College Park, Md.
Collins-Williams, Cecil, 52 East End Ave., Apt. 4-D, New York 28, N.Y.
Comly, Hunter Hall, Children's Hospital, Iowa City, Iowa
Daniel, Roy David, Ferguson Bldg., Sylva, N.C.
Djerf, Charles, 1200 Hancock, Quincy 69, Mass.
Ferris, Benjamin Greeley, Jr., 55 Shattuck St., Boston, Mass.
Gardner, Lytt Irvine, Dept. of Biochemistry, Univ. of N.C., Medical School, Chapel Hill, N.C.
Ginn, Stephen Arnold, Child Guidance Clinic, Duke Hospital, Durham, N.C.
Goldstein, Eugene O., 2412 Eutaw Place, Baltimore, Md.
Hall, William Hugh, Suite 2, Medical Bldg., Charlotte, N.C.
Hankin, Norman Merlin, 462 N. Taylor Ave., St. Louis, Mo.
Hazard, Sprague Whipple, 280 Independence Drive, Chestnut Hill 67, Mass.
Hickman, Thorval L., 2524 Pennsylvania Ave., S.E., Washington, D.C.
Hirsch, Donald Robert, 1 Greenridge Ave., White Plains, N.Y.
Householder, Charles H., 321 S. Bellevue, Memphis, Tenn.
Jordan, Robert G., Jr., 302 S. Washington, Brownsville, Tenn.
Kirchner, Walter Arnold, 3610 Lexington Road, Louisville, Ky.
Koenig, Leonard Joel, Vanderbilt Univ. Hospital, Nashville, Tenn.
Kramer, John Frederick, Veterans' Administration Hospital, Newington 11, Conn.
Little, Joseph A., Children's Hospital, Louisville, Ky.
Lovejoy, George Shannon, 376 S. Bellevue, Memphis 4, Tenn.
Mackler, Bruce, Children's Hospital, Cincinnati, Ohio
MacQueen, John C., Children's Hospital, Iowa City, Iowa
Marino, John J., 5515 W. Dakin St., Chicago 41, Ill.
McGrath, Edward Francis, 27 Otis St., Milton 86, Mass.
McManus, Thomas P., 1 Beaver Lane, Levittown, N.Y.
Morris, C. Christopher, II, Children's Hospital, Galveston, Tex.
Neikirk, William I., Benmoreell Baby Clinic, 200 Helmick St., Norfolk, Va.
Panitz, Philip I., 660 Palisades Drive, Akron 8, Ohio
Paul, John Robinson, Jr., 82 Rutledge Ave., Charleston 37, S.C.
Pitt, C. Kermit, 244 Grant St., Decatur, Ala.
Redner, Bernard, 735 Crown St., Brooklyn 13, N.Y.
Ross, Avron Herbert, 44 Gramercy Park North, New York 10, N.Y.
Russo, John R., 3296 Main St., Bridgeport, Conn.
Sarshik, Milton, 8400 Forrest Ave., Philadelphia, Pa.
Schley, Richard Larcombe, Jr., 114 W. Gaston St., Savannah, Ga.

Silberman, Donald Jared, 1815 11th Ave., South, Birmingham 5, Ala.
Stillman, Norman, 57 Acorn Lane, Levittown, Hicksville, L.I., N.Y.
Sullivan, Daniel Francis, 109 S. Broad St., Mobile, Ala.
Taylor, Fred M., Baylor University, College of Med., Houston, Tex.
Thomas, Helen Yeager, 909 University, Columbia, Mo.
Watson, George A., 1105 W. Main, Durham, N.C.
Wells, C. Robert E., Greene and Coulter St., Philadelphia 44, Pa.
Welty, John Allen, 308 S. Third St., Harlingen, Tex.
Wessel, Morris A., 789 Howard Ave., New Haven, Conn.
Zinzi, Francis L., 2808 S. Randolph St., Arlington, Va.

* * *

Dr. Joseph Stokes, Jr., delivered the Porter lectures at the University of Kansas Medical School on March 13 and 14. The three lectures dealt with the role of a virus laboratory in medical practice, pathogenesis of hepatitis and the use of cortisone and ACTH in pediatrics.

* * *

Dr. Hugh Leslie Moore, Dallas, Texas, died on Jan. 20, 1950. Dr. Moore was a past president of the Southern Medical Association. He also was a member of the Central States Pediatric Society and participated in the formation and establishment of the American Academy of Pediatrics of which he was a Fellow.

* * *

Dr. William Boyd Reading, Galveston, Texas, died on Feb. 2, 1950. Dr. Reading was Professor of Pediatrics at the University of Texas Medical Branch from 1924 until his death. He was a Fellow of the American Academy of Pediatics.

DEAR DR. MCCULLOCH,

The article entitled "Papular Urticaria" by Harvey Blank et al. (PEDIATRICS 5:408, 1950) has been read with special attention to the manner in which DDT is employed for treating the urticaria. May I offer the following comments:

1. DDT in the dry or solid form is not absorbed by the skin. Such preparations may be safely applied provided the dust or powder is not inhaled or ingested during the application.

2. DDT in oil solution or wettable powder form readily penetrates the skin. If the lotion mentioned in the article had contained any oil, alcohol or other solvent for DDT, the daily application of 100 ml. of the 5% preparation could have been dangerous. It is probably a fortunate coincidence that the use of the lotion was abandoned early in this study.

3. Under "Instructions," directions are given to spray the household daily with 5% DDT. DDT is a very effective residual insecticide and one thorough spraying of the house should be effective for at least 3 months and possibly even 6 months to a year. Some modification of the spraying instructions are probably in order.

4. The dusting of household pets presents another problem. Cats are very sensitive to DDT and can be fatally poisoned by a single application of DDT dust. Dogs are less susceptible. It is advisable to employ some other insecticide for these animals. The pyrenones, a combination of pyrethrins and piperonyl butoxide, have been found safe for use on pets.

5. The dusting of beds and bed clothes with 5% DDT dust should be safe provided proper precautions are taken and the dusting is not overdone.

6. As I understand it, DDT is dusted on the patient daily for a period of 2 weeks. Unless there is a specific reason (bathing?) for the repeated treatment I seriously doubt whether these repetitions are necessary. If the household, animals and bed clothes, etc., have been sprayed or treated with DDT there would be little reason for repeatedly exposing the child to inhalation and ingestion hazards of DDT. The effectiveness of DDT as a poison and as an insecticide should not be underrated. It should be added that the use of cosmetics containing grease or oils should not be permitted during the DDT-treatment period.

(signed) A. J. LEHMAN, M.D.
Chief, Division of Pharmacology
Food and Drug Administration, FSA
Washington, D.C.

INTERNATIONAL NEWS AND REPORTS

NEWS FROM ENGLAND

ALAN MONCRIEFF, M.D., *Corresponding Editor*

SCHOOL HEALTH IN ENGLAND AND WALES

The Chief Medical Officer of the Ministry of Education, in his latest report,[1] deals with the 2 years 1946 and 1947. It is appropriate that this should be so, for the 2 year period is one of special significance during which the full implications of the Education Act of 1944 for School Health work were being realised, while the National Health Service was not yet in operation to take its share of the burden. This latter point had considerable influence, for some local authorities were understandably shy of incurring expense in developing school health activities which might prove unnecessary when the National Health Service came into being. The report should, therefore, be read largely as a constructive commentary on a period of advance and experiment.

The first section deals with nutrition. The old system of classifying a child's nutrition as "A," "B," "C" or "D" on general examination had never been popular among school medical officers, who had commented pointedly and at length on the worthlessness of snap judgments on a question which defied precise answer. In 1947 a change was made by which the child's "general well being" was assessed in 3 classes, "A," "B" and "C," "B" being taken as equivalent to "generally satisfactory." It is probable that the previous category "B" referred to much the same general state as the new "B," so that the inference drawn from from the data available, that on the whole the general condition of English and Welsh schoolchildren has improved since 1938, is reasonable. Interesting support is given by the results of height and weight surveys in London and Liverpool. Insofar as such improvement is due to improved nutrition, credit is in large part due to the School Meals Service and the Milk in Schools Scheme. During the 2 years under review, the percentage of pupils having dinner at school rose from 41.7 to 50.8 (since the total school population also rose, the increase in meals served is appreciably greater than this figure would suggest) and the percentage of children having milk reached a steady figure in the region of 88%.

The period was one of special progress in physical education and in the association of this work with remedial exercises for both imminent and established defects. Close co-operation between School Medical Officer, orthopaedic consultant and Organiser of Physical Education is essential and the experience of several pioneer local authorities, quoted in the report, shows what can be done when this is achieved.

A melancholy interest attaches to the short chapter on the School Dental Service. It records that the dental schemes of many authorities suffered during the war by the withdrawal of staff for service with the Forces but that by 1947 the position had so far improved that there was one whole-time dental officer for approximately every 5,500 children. The need for large-scale expansion and improvement is stressed with no prophetic glance to the calamitous days of 1948-1949 in which dentists by the score were to forsake school health work for general dental practice. A brief table sets out the incidence of dental caries in 7 characteristic areas; an over-all percentage of 19.2 children of 12 years of age with no decayed, missing or filled teeth is certainly nothing to be ashamed of, but the fact that the percentage is 8.6 in Manchester and 26.2 in West Sussex gives food for thought. This type of survey is well worth carrying further.

Four special types of defect or, in the new terminology, "handicap," are selected for special comment and in each case a wealth of useful advice is presented in a few pages. The first is epilepsy. The difficulties in the way of diagnosis are indicated and there is a brief sketch of the current trends in treatment. Chief attention is paid to the question of special education. Survey results suggest that children who require special school education because of epilepsy tend to be educationally retarded, with intelligence quotients in the 70-80 region. It is, therefore, suggested that curricula might well have a practical bias and that plenty of attention should be paid to the out-of-hours activities of these children; stress is also laid on the need to educate public opinion to an understanding tolerance of the sufferer, for his own welfare as well as in the best interests of society.

Constructive work with the cerebral palsied child is still something of a novelty in Britain and

the lucid general discussion of the problem in general terms which the report contains is admirably designed and timed. More specific is the chapter on the ascertainment of educationally subnormal children—the 1944 Education Act and regulations made under it have abolished mental deficiency among school children—and its 4 pages of advice to the ascertaining officer can be read with profit by anyone who carries out intelligence tests.

The education of partially sighted children is also extremely sanely dealt with. It is now administratively possible to separate the partially sighted from the blind and 4 boarding schools for the partially sighted have now come into being. "Not only are the parents pleased, but the staffs, freed from the need to consider the requirements of two dissimilar types of child, are able to give all their energies to devising curricula and teaching methods applicable to the partially sighted." Firm and clear guidance is given regarding the education of myopes and the old belief that reading might accelerate the progress of their defect, a belief which has been wearing thin for many years, is at last officially discarded. "Partially-sighted children, myopes as well as non-myopes, may without danger to their eyes read any size of letter which they can see clearly. They may hold the paper or book on which it is written as close to their eyes as they choose, provided they employ binocular vision or have only one functioning eye." Similar advice is given about writing. The use of reading lenses of the type designed by Stockwell in Leeds in 1934 is encouraged.

Among the multitude of other matters dealt with in the report are school medical records, asthma clinics, the place of chiropody in school health work—with some interesting comment on plantar warts—and a full and critical survey of the whole problem of hospital schools. It only remains to add that the report is well written by the anonymous team which presents it and to mention, as Sir Wilson Jameson does, that one of the oldest and most valued members of that team, Dr. J. Alison Glover, whose normal term of service was due to end in 1941 but was extended with his consent, left the Ministry during the period under review.

JOHN D. KERSHAW

REFERENCE

1. Health of the School Child, Report of the Chief Medical Office of the Ministry of Education for the Years 1946 and 1947, London, His Majesty's Stationery Office, 1947.

BOOK REVIEWS

MONGOLISM AND CRETINISM, ed. 2, Clemens E. Benda, New York, Grune & Stratton, 1949, $7.00, 316 pp.

To the scientific investigator the book of Benda's on mongolism and cretinism is of provocative interest but is unconvincing. Unfortunately the writer has presented his own hypotheses in an authoritative manner which may deceive some readers into believing that these have been actually proved and may lead to unwarranted optimism concerning the treatment of mongolism.

Mongolism is the subject given principal attention in the book. Cretinism is considered in contrast to mongolism and little is added to the present knowledge. The author has had a large experience with mongoloid patients and for years has made intensive studies, particularly along pathologic lines. Accordingly his views deserve careful and critical consideration.

In the preface of the second edition Benda is careful to disclaim the theory that prenatal hypopituitarism is the "cause" of mongolism, a deduction which apparently arose from the text of the first edition, and states that mongolism is due to "a constellation of certain adverse factors which operate in the maternal organism and deprive the growing embryo of a proper nutritional environment." He states categorically that it is not due to a genetic mutation or an abnormal ovum and in Chapter X attempts to build up the hypothesis that there is an endocrine abnormality of the mother during pregnancy, although no studies have been made to support this. To explain the occurrence of mongolism in only one of a pair of twins (Watson has recently collected 82 instances, as reported in the *American Journal of Diseases of Children*), Benda suggests (p. 251) that "if the deficiency of the mother which leads to mongolism in her offspring is very severe, both babies may be affected, while in a deficiency of moderate degree one twin may be spared while the other becomes abnormal." If the reader is dissatisfied with this reasoning he is offered a hypothesis of superfecundation.

Having attributed the cause of mongolism to a maternal abnormality, Benda devotes most of the book to the thesis that the developmental anomalies of the "ill-finished" child are due mainly if not entirely to hypopituitarism beginning in early embryonic life. The physical characteristics of mongolism, described as "congenital acromicria," are naïvely contrasted with acromegaly. The persistence of the developmental retardation is pictured as due to lack of the pituitary hormones in both the prenatal and postnatal period. In a chapter devoted to a description of the pathologic changes in the nervous system, Benda disregards the possibility that the congenital brain defect may be merely one of a number of associated developmental anomalies in the syndrome. He concludes that "the mental deficiency is the result of a chronic deficiency of oxygenation or sugar metabolism" (p. 97), basing this hypothesis largely on his histologic studies.

Benda's concept of mongolism as primary hypopituitarism accompanied by secondary deficiency of the thyroid, adrenals and gonads is based entirely upon the histologic changes in the endocrine glands, particularly the pituitary, which are described in Chapter V. The pituitary presents a variety of different pictures but in general the glands show either a predominance of eosinophils or a predominance of chromophobe cells with a deficiency of gamma cells. To fit in these findings with the concept of hypopituitarism, Benda does not hesitate to discard the previous theories concerning pituitary histology and to substitute a new theory of his own. The thyroid glands in some mongols are shown to be quite small compared to the normal size for the age, but this is most apparent in the patients over 12 years (who are small individuals anyway). There is no uniformity of the histologic picture of the thyroid. Although Benda interprets the pathology as indicating a resting gland due to lack of thyrotropic stimulation, he describes 20.8% of the cases as having "colloid goiter with signs of possible toxic activity" (Table 13). The adrenals are described as showing persistence of the fetal cortex. Anomalies in sexual maturation of mongoloid males and females are common. In 9 males over 16 years of age Benda describes a number of different types of testicular atrophy and attempts to correlate these with the type of pituitary histology and presumably with a deficiency of either FSH or LH. Likewise, there was no uniform type of ovarian pathology and in some cases the ovaries were normal. The report by Dr. Grace Sawyer of a mongoloid mother who gave birth to a normal child is mentioned.

Benda has performed a service in reporting in detail his pathologic and clinical findings but he has shown an unwarranted boldness in interpreting the histologic characteristics of the endocrine

glands in terms of their secretory activities. There is still no agreement among endocrinologists concerning the relationship between the various cells of the pituitary and their hormonal secretions. The author's theories of pituitary physiology can be neither denied nor proved. It seems quite certain that various abnormalities of the endocrine glands were found in the autopsies of mongols but Benda does not present data concerning the terminal illness and nutritional condition of his patients to establish the fact that the endocrine atrophy was not secondary to a systemic disorder. The existence of endocrine dysfunctions can be established only by the demonstration of functional disorders during life employing the newer methods of hormonal studies. The biochemical studies which Benda marshalls in Chapter IX offer no real support of his claim of hypopituitarism with other glandular deficiencies occurring secondarily. The response to insulin was not unusual, the curves rising promptly 20 to 30 minutes after injection (p. 235). The values for serum cholesterol (Table 29) were not abnormal. The excretion of urinary "androgens" (presumably the writer meant 17-ketosteroids) was within the normal range up to 14 or 18 years of age but in some of the male adults the excretion remained at this comparatively low level. Benda interprets this as indicating a normal production of adrenal androgen and a deficiency of gonadal androgen. As a matter of fact these findings are against hypopituitarism as the cause of hypogonadism and suggest that pathologic changes of the gonads described in Table 15 may be primary testicular defects. The question could probably be settled by bioassays of the urinary gonadotropins but unfortunately this test, which is now employed by every endocrinologist in studying the etiology of hypogonadism, was not made. Even if it is proved that mongols have certain abnormalities of their endocrine glands the possibility that these are merely anomalies associated as part of the congenital syndrome rather than the primary cause of the developmental disorders can scarcely be denied.

As a result of his belief that mongols have deficiencies of the pituitary and thyroid, Benda advocates treatment with thyroid substance and "growth hormone" if it were available. Pediatricians who have had the opportunity of seeing mongoloid children who have been treated intensively with thyroid for years will derive little optimism from this advice. The data given in Figure 104 shows that at the age of 14 years the maximum mental age of the mongols treated with thyroid was 7 years as compared with 5 years in the untreated and this does not take into consideration possible improvements of environmental and educational factors in the treated group. We agree with Benda that no efficient pituitary treatment is available at present. Even the newer purified preparations of growth hormone which have been effective on rats have failed to produce growth in humans.

ED. NOTE: The second edition of this book has been given unusual handling in preparing a review. It has been felt that a book so full of danger should be commented on even though the editorial policy is not to publish reviews of books which deserve unfavorable comments or to review subsequent editions of books at length.

MORBUS CAERULEUS, edited by E. Mannheimer, M.D., Basle and New York, S. Karger, 1949, $9.25, 332 pp.

This symposium on cyanotic congenital heart disease is by several Swedish authors. The contents include an excellent brief review of the embryology of the human heart and blood vessels, clinical analysis of 114 cases which form the basis of the monograph, and detailed laboratory studies of some of these cases. The studies include a rather complete consideration of conventional roentgenologic examination and angiocardiography, a chapter on ECG and one on cardic catheterization as a diagnostic aid. Studies of function include an attempt to apply an hypoxia tolerance test but uniform ECG changes were not found. The standard exercise tolerance test of Cournand and Richards was compared in 15 normal children, 18 cases of patent ductus arteriosus, 12 instances of tetralogy of Fallot and 3 cases of the Eisenmenger syndrome. The findings in the latter group were not in accord with the report of Bing, Vandam and Gray. Studies of the circulation time by the fluorescin method are reported. The application of calibrated phonocardiography, developed by Mannheimer, is described and the results in 103 cases reported. Surgical and postoperative treatment is briefly considered. An appendix with essential details of the cases reported and a bibliography completes the book.

Although not as complete as Taussig's "Congenital Malformation of the Heart" or as specialized as Cournand, Baldwin and Himmelstein's "Cardic Catheterization in Congenital Heart Disease," this monograph brings together for the first time in one volume modern clinical interpretation and diagnostic technics related to cyanotic congenital heart disease. It is not only an excellent review of the

embryology and clinical manifestations of this type of heart disease but, because it reports detailed studies of specific cases, it is an important contribution of permanent value.

The format and illustrations are unusually good. The monograph is a valuable addition to recent studies of this subject, and is especially suitable to those who require a single volume review of the modern concepts and diagnostic procedures related to cyanotic congenital heart disease.

BEDSIDE PHYSIOLOGY, Rudolf Engel, M.D., Munchen, Urban & Schwarzenberg, 1949, DM 20, 246 pp.

This book on applied physiology fills a gap in postwar medical education in the German-speaking area. It informs the German student regarding the progress made in the English-speaking world and will be especially welcomed by him because from the didactic standpoint it is written simply and is well illustrated. It contains what most students in the clinical field want to know when they relate their bedside problems to underlying physiologic principles. It also focuses attention on important clinical problems. Clinical experience is necessary in order to teach bedside physiology adequately. Since the publication of the famous textbook by Krahl, successive textbooks on applied physiology have been written by clinicians to bring the subject up to date periodically. Engel's textbook is brief, and compact, but it fulfills its purpose very well. Sixty well selected illustrations supplement the text material. An English edition would be welcome.

ADRENAL GLAND, Frank A. Hartman, Ph.D., and Katharine A. Brownell, Ph.D., Philadelphia, Lea & Febiger, 1949, $12.00, 581 pp.

This volume is particularly timely in view of the upsurge in interest in the adrenal gland as a result of the discoveries of Hench and co-workers. It represents a huge task in bringing together a large part of this voluminous literature.

The 34 chapters cover a wide range of subjects from the anatomy and chemistry of the gland to clinical syndromes associated with disturbances in function. A great deal of valuable information on the comparative function in different species is included. Unlike many recent treatments of this subject, the adrenal medulla has not been overlooked in this volume.

The book excels as a compilation of literature rather than as a lucid synthesis of the known facts. Its use as a reference book should prevent the needless repetition of published experiments. The 120 page bibliography and excellent index add greatly to its value.

DIAGNOSIS AND TREATMENT OF ADRENAL INSUFFICIENCY, George W. Thorn, M.D., Springfield, Ill., Charles C Thomas, Publisher, 1949, $5.50, 171 pp.

This volume represents a valuable addition to the monograph series in endocrinology. It is a simple lucid exposition of both the principles and details of treatment of adrenal insufficiency. It is written primarily from a didactic rather than scholarly point of view and should be of great use to students, house officers and practitioners in the diagnosis and care of patients with adrenal insufficiency. From the point of view of the expert, it represents a valuable summary of the extensive experience of Dr. Thorn and his associates.

FOR THE NEW MOTHER, Mildred V. Hardcastle, R. N., Philadelphia, John C. Winston Company, 1949, $2.00, 163 pp.

It is refreshing to find a book which is medically and psychologically sound and at the same time written in a warm, friendly, reassuring vein. Mothers and mothers-to-be will surely be convinced that having a baby, watching and guiding his growth and development, can and should be a joyous happy experience. The author, a mother herself, writes with real understanding, born of experience in meeting the situations which can be perplexing to the new mother. Her advice is down-to-earth and the common sense suggestions she offers will find a grateful response in readers with a "need to know what to do."

The arrangement of the book is good, progressing chronologically from month to month. It probably would add to the usefulness if there were an early chapter on preparation for the baby. This could contain such things as lists of equipment and utensils needed and a basic layette, as well as the values of mothers' and fathers' classes, a visit to the hospital maternity unit, and early acquaintance with the pediatrician of choice.

In light of much of the present day thinking and studies done, more careful discussion should be given to breast feeding. The title of the chapter "Making the Formula" sets the emphasis on bottle feeding and of the 14 pages in this chapter only 2 brief paragraphs describe, somewhat vaguely, the advantages of breast feeding.

The stressing by the author of individual patterns, rather than development of habits, and the advice that each mother study and anticipate the "natural development pattern" of her own baby rather than compare with the progress made by her neighbor's children are excellent. The admonition to build from the beginning toward the goal of a happy, healthy, well adjusted child, by looking ahead and trying to choose the smooth way where issues seem to arise, and to plan for learning by gradual adjustments without emotional issues are practical workable suggestions bound to bring desirable results.

The final discussion of the confusions so often caused by modern psychology versus old fashioned child training is well handled and should rid the minds of new mothers of much conflict and confused thinking.

The book is exactly what the title implies, a guide for the new mother or mother-to-be, written simply and understandably and in a delightfully informal way.

PHTISIOLOGIE INFANTILE, Pierre Lowys, Paris, Flammarion & Cie, 1948, 2120 francs plus 180 francs postage, 700 pp., 220 figures.

This is an encyclopedia of 700 pages on pulmonary tuberculosis in children. Every aspect of chest disease as it occurs in the first 2 decades of life is described completely and clearly in the French language. It is fascinating reading for one interested in tuberculosis. An English translation would be of great value. The vast experience of the author and large number of cases upon which he has been able to draw will add much to the knowledge and understanding of tuberculosis though the reader will disagree with some of the methods employed and some of the conclusions arrived at. The subject matter is divided into 7 parts: generalities, clinical aspects, diagnosis, medical treatment, pneumothorax and collapse therapies, surgical treatment, and hygiene and prophylaxis. The author considers the disease as passing through 3 stages in somewhat the same way as syphilis. These stages are not very clear cut nor easy to differentiate and differ from the concept of the disease as primary infection and reinfection disease. He speaks of the primo-secondary stage, which is rather confusing. The clinical aspects of pulmonary and mediastinal disease is dealt with in detail. Many case histories illustrate the text and add to its interest. There are numerous roentgenograms shown.

In the chapter on diagnosis the tuberculin test is particularly interesting and practical. The behavior of this reaction in the progress of the disease as it affects the allergic response of the skin to tuberculin is described in great detail.

Medical treatment covers all the organized medical care and, in addition, several less well accepted treatments such as gold salts. None of the newer, more specific, medications, neither streptomycin nor sulfa drugs, are mentioned. The chapters on pneumothorax are of special value. It is covered from every standpoint and is well illustrated by cases and roentgenograms. This method of treatment has been used extensively and is strongly advocated for the treatment of many types of pulmonary lesions with active disease. For anyone who is in this field of work this section is invaluable.

This medical volume is not only a scientific work but is filled with the art of medical practice. Seldom does one find so much of value condensed into one volume. It should be owned by everyone in this specialty and should be read by all pediatricians.

ACUTE LARYNGOTRACHEOBRONCHITIS, A. Harry Neffson, M.D., New York, Grune & Stratton, 1949, $5.00, 197 pp.

This small volume fills a long-felt need in medical literature for the presentation in one place of the accumulated knowledge on this subject. The author is by training (otolaryngology) and special interest well qualified to present the material. Lest a pediatric audience approach the book with suspicion, the following quotation should be noted (p. 157): "I feel that in most cases the pediatrician should assume the direction in the handling of these patients, except for the endoscopic and surgical aspects, which are obviously the proper domain of the laryngologists."

The book contains 13 chapters which discuss separately various aspects of the disease, such as

pathology, bacteriology, diagnosis and treatment. There is a commendable chapter devoted to the confusion in terminology, as well as a chapter on "The Role of the General Practitioner, the Pediatrician, and the Otolaryngologist." A separate chapter on tension pneumothorax and mediastinal emphysema after tracheotomy is excellent. In his discussion of methods of treatment the author strongly and lengthily defends intubation, but rules out much of his dicussion for the general medical audience by stating, wisely, that intubation should never be undertaken unless specially trained residents or attending physicians are immediately available at all times. Much of the specific data in the book is drawn from the author's personal experience.

The discussion of differential diagnoses is too cryptic. The chapter on bacteriology is not well organized, but it does emphasize our lack of knowledge concerning the primary agent in the disease. The discussion of supraglottic edema, to which an entire chapter is devoted, is confusing. The author minimizes the importance of H. influenza type b as a very common etiologic agent of supraglottic swelling—although the recent literature is strongly against such a stand. In some instances statements are made which would offend the sensibilities of most pediatricians, i.e., Baum's contention that hypertonic albumin will reduce localized laryngeal edema, and the incrimination of an enlarged thymus in some cases of upper respiratory tract obstruction. There is a large bibliography, an author index and a subject index. The book is well published but stingily illustrated. In the reviewer's opinion this small volume should be read by all pediatricians who have occasion to handle cases of "croup."

In Memoriam

JOHN A. TOOMEY

JOHN TOOMEY died January 1, 1950. Born May 25, 1889, his preliminary education was in law, in which he received the degree of LL.B. and he practiced law for one year. Forsaking law for medicine, he entered medical school and received his medical degree from Western Reserve University in 1919. His entire professional career was devoted to the service of his Alma Mater where, beginning in a minor capacity, he had steadily increasing responsibilities to be finally Professor of Clinical Pediatrics and Contagious Diseases, Western Reserve University School of Medicine, and Associate Director of Pediatrics and Contagious Diseases and Associate Director in the Department of Pediatrics, Out Patient Department, City Hospital of Cleveland.

An inspiring teacher, his precepts have influenced a great many whose interests fall within his chosen field. His sound clinical judgment and experience in pediatrics, especially in the field of communicable diseases, were combined with an inquiring and imaginative approach to laboratory experimentation in which he did not hesitate often to depart from the beaten track. His interests were many and varied and he made great contributions to pediatric knowledge. Some three hundred papers attest his productivity in his chosen field. He was a pioneer in virus research particularly, of course, with reference to poliomyelitis, in which his resourceful experimental approach was best exemplified.

He had unceasing interest in the Academy from the time of its organization and contributed unstintingly to the scientific program, to round table and panel discussions, and to committee activities, especially the Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases, of which he was for many years the chairman. His election to the Presidency of the Academy in 1948 was the natural culmination of his intense interest in our organization. Well known to the membership of the Academy, he had a wealth of warm friendships and his forthrightness and stubborn uncompromising honesty won him the respect and admiration of all and the sincere affection of those who knew him best.

For John Toomey there could be no better memorial than to be remembered for those very things which he himself held most dear.

E. B. SHAW, M.D.